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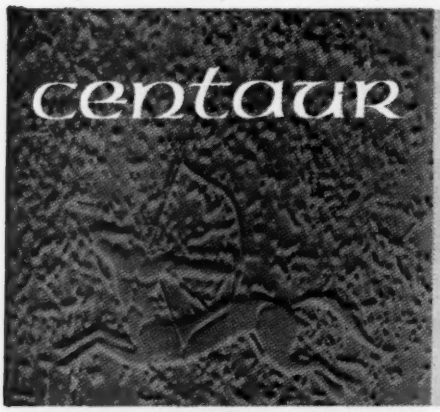

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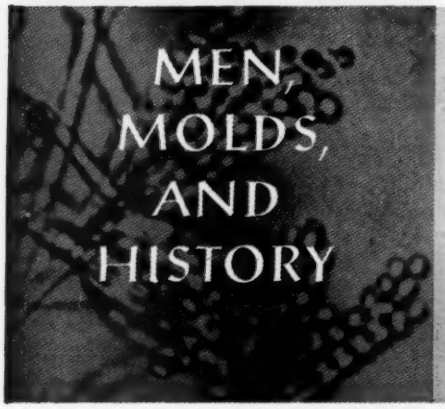

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Evaluation of a Combination of Meclizine and Pyridoxine in the Control of Nausea and Vomiting in Pregnancy

R. C. Bethea, M.D.

MEMPHIS, TENN.

Nausea and vomiting are symptoms that occur so often during the first three to four months of pregnancy that they are considered by many women to be a normal accompaniment of the condition. While at times the symptoms may be so mild as to cause little annoyance, frequently they assume such proportions that for weeks the woman is incapacitated. Occasionally they may persist and assume dangerous proportions in the syndrome known as hyperemesis gravidarum.

The etiology of the nausea and vomiting of early pregnancy is poorly understood. Since there is an increase in estrogen during the weeks after conception, and since massive dosages of exogenous estrogens will frequently cause nausea or vomiting in nonpregnant persons,[1, 2] this has been considered by some to be responsible. Others have felt that the decidual reaction produces toxic materials that initiate the symptoms.[3] The increase in the enzyme histaminase in the blood of pregnant women has been interpreted by others as indicating that the vomiting must be due to an increased quantity of histamine liberated during pregnancy.[4] Some feel that the nausea and vomiting are largely psychological in origin.[5] There is evidence that during pregnancy a deficiency of pyridoxine develops and this is sometimes considered to be the etiological factor.[6]

Whether one or a combination of these components is responsible for the development of these symptoms is a question that cannot be answered conclusively. No form of therapy directed at one presumed cause has been completely effective, yet all have enjoyed some success. Anticholinergic agents, such as atropine and scopolamine, have been used for years with only moderate benefit and a rather high incidence of side effects. The newer anti-motion sickness drugs have been of some apparent value, but by themselves are no more effective than the anticholingergic compounds. Central nervous system depressants help some patients, but near-hypnotic doses usually are required. Many of the antihistamines have been of no value, although some of the anti-motion sickness drugs do possess marked histamine-blocking prop-

erties.[7] The relationship between histamine antagonism and antiemetic action is obscure at this time.

Chlorpromazine, a drug that possesses anticholinergic, antihistaminic, and central nervous system–depressing actions, has been reported to be of great value,[8] but recent reports have indicated that untoward toxic reactions in the form of liver, kidney, and bone marrow damage may occur.[9]

Pyridoxine (vitamin B_6) deficiency is concerned with the deamination and decarboxylation of amino acids. Studies of patients with severe vomiting in pregnancy have disclosed blood chemistry changes indicative of pyridoxine deficiency, and administration of this substance has both corrected the blood chemistry picture and alleviated the vomiting.[6] Yet its use alone has not always helped.

Recent reports have indicated that Bonadoxin,* a preparation containing 25 mg. of meclizine and 50 mg. of pyridoxine per tablet, may be more effective, with fewer undesirable or toxic effects, than any form of treatment to date.[10, 12, 17, 18] Meclizine is p-chlorobenzyhydryl-m-methyl-benzyl piperazine dihydrochloride. It is a potent antihistaminic agent and possesses moderate acetylcholine-blocking activity. In animal experiments meclizine was found to have a low degree of toxicity.[13] It is unique among compounds of this type in that it has a very long duration of action.[7] It has been reported to be of value in nausea and vomiting of pregnancy and motion sickness.[7, 14, 15]

The value of pyridoxine in some cases of vomiting in pregnancy is well established.[6, 16] The combination of these two substances seemed to offer promise of more effective control of the distressing symptoms associated with early pregnancy. Preliminary experience has borne out this hope.

EXPERIMENTAL STUDIES

One hundred and five patients from 19 to 40 years of age, with the majority between 21 and 30, were treated with the combination drug. All complained of severe nausea and vomiting when first seen. The drug was administered as indicated in table I.

Results were termed "excellent" if no disturbances referable to the gastrointestinal tract were noted during therapy. If vomiting and severe nausea were controlled, but slight "morning sickness" persisted, the drug effect was considered to be "good." If, in spite of therapy, there was a persistence of the symptoms, the response was described as "poor."

RESULTS

Initially, two dosage schedules were followed. One group of patients were told to take 1 tablet daily on retiring. Patients in the other group took the drug three times a day. Of the first group, 5 patients felt they obtained better control of the symptoms when they took an additional tablet in the morning, and of these, 2 were

* The trade name of J. B. Roerig & Co. Division, Chas. Pfizer & Co., Inc., for a combination of meclizine and pyridoxine is Bonadoxin.

TABLE I

Results of Therapy with a Combination of Meclizine and Pyridoxine

Frequency of administration	Results*		
	Excellent*	Good	Poor
Once daily	17	11	2
Twice daily	6	14	2
Three times daily	17	22	10
Four times daily	1	2	0
As needed	1	0	0
Total	42	49	14
Per cent of total	40	48	12

* Excellent: No nausea or vomiting after institution of therapy. Good: Mild occasional nausea but no vomiting while on therapy. Poor: Some nausea and occasional vomiting persisted despite therapy.

completely relieved. One patient of this group took the medication only when nauseated and obtained prompt and complete relief.

Two of the patients in the group receiving the drug three times a day felt that taking an additional tablet afforded greater benefit. Both, however, continued to have mild morning nausea.

Of the entire group, 40 per cent had excellent results. Forty-eight per cent obtained almost complete relief from the severe nausea and vomiting, although they had occasional mild discomfort early in the morning. Of this group, all were able to continue their work or household duties without loss of efficiency. Many felt that without the drug they would have been incapacitated. Seven, who had suffered markedly in previous pregnancies, obtained prompt and dramatic relief—more than from any previous medication they had received.

TABLE II

Duration of Therapy with a Combination of Meclizine and Pyridoxine

Duration, weeks	Results		
	Excellent	Good	Poor
1	4	5	3
2	7	6	2
3	6	7	1
4	8	14	2
5	1	4	1
6	7	4	1
7	1	0	1
8	5	5	1
12	3	4	2
Total	42	49	14

Fourteen women, or 12 per cent of the total, continued to have disturbing symptoms in spite of treatment. It was not possible to ascertain whether their nausea and vomiting would have been worse had the drug not been given. Several, however, had a previous history of being unable to tolerate any oral medication, and failure to respond was not altogether unexpected.

Where practicable, the drug was discontinued at regular intervals; thus each patient acted as her own control. In some cases there was no recurrence of the complaint. In others, nausea and vomiting recurred only to disappear when the drug was taken again. The data in table II, therefore, reflect the duration of the severe discomfort. In most instances the complaint had disappeared within four weeks.

No side effects referable to the medication were noted by any of the patients.

DISCUSSION

Our investigation of this drug indicates that in 88 per cent of the cases satisfactory relief of the distressing symptoms of early pregnancy was obtained without undesirable side effects, including sedation. This degree of successful therapy corresponds to that already reported.[10, 12, 17, 18]

It seems reasonable to assume that the high incidence of success with this preparation is in part due to the combination of two agents. There is little reason to assume that all nausea and vomiting of pregnancy stems from a common cause. Since several physiological and biochemical mechanisms have been implicated in the etiology of the condition, therapy directed at one specific mechanism may be of little value in some patients.

If meclizine acts to depress the sensitivity of the vomiting center to noxious stimuli, as has been postulated,[7] it would be effective in those persons in whom this component was dominant. On the other hand, correction of a pyridoxine deficiency in certain patients would remove a separate etiological mechanism. Since it is practically impossible to identify the cause in a given patient, a combination therapy would be expected to be effective in more patients.

Although the groups were small, it appears that 1 tablet a day may be as effective as more frequent administration. This is not unexpected since meclizine exerts its effects for 24 hours or longer. In those patients who did better on more frequent administration, it is possible that a pyridoxine deficiency played a more important role in their sickness, necessitating more frequent doses of that substance.

This new combination seems to offer definite advantages in the control of the disturbing symptoms of nausea and vomiting in early pregnancy.

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For many years the barbiturates and their derivatives have been the drugs of choice in the treatment of diseases of emotional origin as well as in the management of organic conditions in which stress and anxiety play an important role. Since their introduction, ataractic drugs have been used successfully to allay emotional disorders in this "decade of anxiety." However, both these types of sedatives have produced all too familiar toxic reactions. Barbituric acid preparations exert a toxic effect on liver cells. Their slow excretion results in accumulated toxicity, manifested by symptoms ranging from simple oversedation, headaches, and rashes to more serious conditions of delirium and addiction.[1, 2] While the ataraxics have not been reported to cause serious habituation, many untoward reactions have been attributed to them, i.e., jaundice, agranulocytosis, angioneurotic edema, urticaria, purpura, fever, and vascular collapse.[3] A recent study[4] has shown that ataractic agents can reduce the radioactive (I^{131}) uptake of the thyroid gland in patients whose determinations are higher than the expected normal range. All the patients in this study were tense and had tachycardia, yet did not have clinical thyrotoxicosis.

Methyprylon,# a nonbarbiturate sedative and hypnotic, has proved to be of low toxicity in animals and clinically safe and mild as well as therapeutically effective.[2, 5, 6] In mice and rabbits the drug was found to be distinctly less toxic than phenobarbital. Blood picture studies after prolonged administration to human subjects revealed no impairment of renal function or other untoward effects.[7] No liver function changes were noted after eight weeks of treatment.[2] Electrocardiographic studies on chronic cardiac patients revealed no evidence of effect on the heart.[8]

Up to 12 per cent of methyprylon and its dehydrogenated metabolite (tetrahydropyridine) is excreted in the urine within 48 hours.[9] Dosages up to 1000 mg. daily have been tolerated by human subjects for as long as 105 days.[10] Whereas 15 to 20 times the ordinary hypnotic dose of barbiturates causes severe poisoning, ingestion of up to 100 times the hypnotic dose of methyprylon in suicidal attempts was fol-

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# The trade name of Hoffmann-La Roche, Inc., for methyprylon (3,3-diethyl-2,4-dioxo-5-methylpiperidine) is Noludar.

lowed by uneventful recovery of the patients. This may possibly be due to the lesser tendency of methyprylon than of barbiturates to produce respiratory depressions.[11] In a study of 510 ambulatory patients, methyprylon had a relaxing effect on all patients without causing oversedation.[7] The sleep induced by methyprylon has been reported to resemble the pattern of smooth and natural sleep.[12]

We have felt that relieving emotional tensions in patients with organic or psychogenic diseases will improve the prognosis of the underlying condition. The requirement of a daytime sedative, especially in outpatients, is that it causes little or no impairment of attention or ability to concentrate. It should inhibit agitation only sufficiently to produce normal relaxation with a minimum of unpleasant side effects. For nighttime sedation, the ideal medication is one that produces sound, but not excessively prolonged sleep from which the patient awakens feeling refreshed.

Since methyprylon seemed to meet these criteria as nearly as could be expected of any drug, we conducted a study of its effect on a large group of patients with neurogenic conditions and organic diseases complicated by functional disorders. We also administered it, in larger dosages, to a small group of patients with serious sleep problems.

METHODS AND MATERIALS

Before starting the larger study it was decided to determine the effect of methyprylon on the I^{131} uptake of the thyroid gland. Ten patients underwent 24-hour I^{131} uptake studies prior to the administration of the drug. Doses of 50 mg. four times daily were then administered for 14 days. The I^{131} uptake tests were repeated. The results are given below.

Methyprylon was administered as a sedative hypnotic to 1131 adult patients with organic diseases complicated by functional disturbances, or with functional disturbances alone. These patients were treated in a hospital or on an outpatient basis through private practice or medical and thyroid clinics. A total of 885 patients had functional disturbances associated with organic or infectious diseases including the following: hyperthyroidism, hypothyroidism, disturbances of the cardiovascular, gastrointestinal, or neuromuscular skeletal systems, disorders of a gynecological or urological nature, and infectious diseases, including those of the upper respiratory tract (table I). The remaining 246 patients had emotional disturbances alone, which included: anxiety states, neurocirculatory disturbances, hysteria, and cardiospasm (table II). The drug was administered orally in 50 mg. tablets four times daily. In 14 patients the medication was reduced to half that amount because they became drowsy. Blood counts and urinalyses were performed at specified intervals during the study, which covered a 15-month period. Evaluation of results was based on the quality of relief obtained—excellent, good, or negligible.

A third study was conducted in which methyprylon was administered as a soporific to 25 persons with chronic insomnia, for periods ranging from 14 to 21 days. The dosage was larger than that in the other studies, the drug being administered at bedtime in a 300 mg. capsule. Results of medication were expressed in terms of length of time between administration and induction of sleep and of the duration of sleep.

TABLE I

Methyprylon in Organic Diseases with Associated Functional Disturbances

Disease	No. of cases	Relief		
		Excellent	Good	Negligible
Hyperthyroid conditions (thyrotoxicosis [Graves' disease])	310		310	
Hypothyroid conditions	151		140	11
Cardiovascular disorders (especially hypertension, coronary thrombosis, coronary insufficiency, arteriosclerotic heart disease)	122	30	88	4
Gastrointestinal disorders (peptic ulcer, hiatus hernia, cirrhosis, gastritis)	76	16	48	12
Neuromuscular skeletal disorders (fibrositis, myositis, torticollis, back pains, arthritis)	71		60	11
Gynecological disorders (pelvic inflammation, menopause)	66	3	59	4
Infectious diseases	38	16	22	
Upper respiratory disorders (infectious, asthma, emphysema)	35	18	15	2
Urological disorders	16	8	7	1
	885	91	749	45

RESULTS

Methyprylon did not cause any appreciable change in the I^{131} values of the 10 patients tested; therefore, based on these results, it may be concluded that the drug can be safely employed as an adjuvant in thyroid disease.

All patients to whom methyprylon was administered to relieve tension reported subjective improvements. Outwardly they appeared more calm. Of the 885 patients with organic diseases, 91 had excellent relief of symptoms and in 749 there was a good response to the drug, indicating an over-all benefit of 95 per cent. In 45 cases the relief was so transitory that results have been listed as negligible. In the 246 patients with purely functional disorders, 224, or 91 per cent, had a good response to methyprylon and 22 patients had no lasting relief of symptoms. Aside from the 14 patients whose medication was reduced because of drowsiness, there were no other adverse effects.

Methyprylon produced satisfactory sleep in 22 of the 25 persons with insomnia. The average induction period was 45 minutes and the average duration of sleep

TABLE II

Methyprylon in Functional Diseases

Disease	No. of cases	Relief		
		Excellent	Good	Negligible
Anxiety states	114	—	111	3
Neurocirculatory (asthenia)	60	—	55	5
Hysteria (with conversion)	46	—	37	9
Globus hystericus	5	—	4	1
Cardiospasm	21	—	17	4
	246		224	22

between 5½ and 6½ hours. None of these patients complained of a "hang-over." The remaining 3 patients had an average of 2½ to 4 hours of sleep and considered the drug unsatisfactory.

DISCUSSION

While sedative and hypnotic drugs are not administered for possible curative effects on the organic disturbances per se, they do relax tensions. This effect, in turn, permits the body to make better adjustments and to respond to treatment of the basic condition. The more than 300 preparations on the market containing barbiturates[13] attest to their extensive, almost universal use. The barbiturates have both a sedative and a hypnotic effect, the difference between these actions being one of degree.[14] The only drawback to their use is the side effects, which often are of a serious nature, at times sufficient to make the "cure worse than the disease itself." In recent years the ataraxics have cut down the use of the barbiturates. The ataraxics produce sedation without drowsiness and their side effects are less serious;[14] however, they too exert adverse effects. Therefore, the search for a more nearly ideal drug continues.

Methyprylon, a piperidine derivative, is not related structurally to either the barbiturates or the ataraxics. As with the barbiturates, the difference between methyprylon's sedative and hypnotic effects is one of degree. For daytime sedation, in the group studied, it produced a calming effect without interfering with the patient's acuity. As a soporific it permitted satisfactory sleep. The most gratifying aspect of methyprylon administration was the almost complete absence of side effects. The few cases of drowsiness encountered responded well to a reduction in dosage.

SUMMARY

In 10 patients, prior to and after administration of 200 mg. of methyprylon daily for 10 days, no appreciable difference was observed in I^{131} uptake.

Methyprylon, 50 mg. four times daily, relieved tensions and thereby alleviated

symptoms in 91 per cent of 885 patients with organic diseases and 246 patients with disturbances of a purely psychogenic nature.

As a soporific agent, methyprylon, 300 mg. at bedtime, produced satisfactory sleep in 22 of 25 persons with insomnia.

Methyprylon appears to be an effective sedative and hypnotic agent, free of undesirable side effects and with good therapeutic activity.

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Medical Directory of South Africa Soon to Be Available

The first edition of the *Medical Directory of South Africa*, which has been compiled with the cooperation of the Medical Association of South Africa, will soon be off press, it was announced recently. The *Directory* contains detailed professional biographies and provides the only compendium of medical practice in South Africa, including data on administration, university medical schools, colleges, research institutions, and hospitals. Fully bound in dark blue rexine with a gold-blocked cover, the book contains more than 400 pages and is 9½ by 6 inches in size. Retail price of the *Directory* is $7.50 (subject to any fluctuation in exchange rates), plus $1.00 for postage.

Relative Merits of Mouth-to-Mouth Resuscitation

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The need for an efficient and simple method of artificial respiration has been intensified by the realization that mass casualties might develop from modern scientific weapons in the event of war. The manual methods of artificial respiration have been subjected to scientific evaluation and found to be quite efficient for the purpose, so much so that as a result of these tests, the back pressure–arm lift method has been adopted and universally recommended for artificial respiration. It was not fully realized at the time of evaluation that the testing conditions were ideal. By this was meant that all the subjects were completely paralyzed, and all were provided with an almost ideal airway—the endotracheal tube. Under these conditions it was demonstrated with the manual methods of artificial respiration, primarily the Holger-Nielsen or back pressure–arm lift method, that sufficient amounts of air may be moved back and forth through the patent airway of the subject. Unfortunately, when these same methods were evaluated without the endotracheal tube and without the flaccid paralysis provided by curare, manual artificial respiration proved inadequate in the unconscious patient. It was observed that upper airway obstruction developed frequently and interfered with the efficiency of the method.

One of the oldest methods of artificial respiration, which is still occasionally employed in infants and children, is mouth-to-mouth breathing. The very term itself conjures visions of intimacy between the rescuer and rescued so that the method frequently evokes the repugnance of the fastidious. However, the mouth-to-mouth method of artificial respiration has been known for a long time and may be traced back to antiquity. It is mentioned in the Bible and has frequently been referred to as the biblical method of resuscitation. Various modifications of this method of artificial respiration have been described recently in the literature, and an all-inclusive term has been devised to cover all these various modifications, i.e., expired air inflation or ventilation. Aside from direct mouth-to-mouth inflation, the other methods are the mouth-to-nose, mouth-to-mask, mouth-to-oropharyngeal airway, mouth-to-endotracheal tube, and mask-to-mask methods. Some of these techniques may be combined, e.g., by inserting an airway into the oropharynx, then placing a face mask over the mouth and nose and blowing into this apparatus.

PHYSIOLOGICAL CONSIDERATIONS

In order to determine the effectiveness of any method of artificial respiration, two factors must be taken into consideration, namely, the efficacy of the method on the subject and the ability of the rescuer to apply the method continuously and effectively without fatigue. Therefore, there are three things to be determined in relation to these methods to prove their value: the oxygen concentration in both the patient

and the rescuer, the carbon dioxide concentration in both the patient and the rescuer, and the physical ability of the rescuer to ventilate the subject.

Oxygen Concentration. Considering the fact that expired air discarded by the rescuer is used in resuscitation, there immediately arises the thought that this may be unphysiological. Also, associated with this concept of expired or discarded air is the belief that the amount of oxygen in expired air has been appreciably diminished and that there is a marked increase of carbon dioxide, which is waste material coming from the person discarding the expired air. Thus the physiological soundness of the method immediately evokes skepticism. An examination of oxygen concentration in the rescuer's expired air and the patient's arterial blood during the process is in order. A normal adult breathing 20 times/minute with a tidal volume of 500 ml./breath will have a minute volume of 10 liters or 10,000 ml. Atmospheric air at sea level or inspired air has a concentration of 20 to 21 per cent oxygen. Thus, of the 10,000 ml. that a normal person inhales within a period of one minute, 21 per cent is oxygen, which amounts to about 2100 ml./minute. It has been shown that the average adult normally requires 300 ml. of oxygen per minute for metabolic purposes. Thus, 1800 ml. of oxygen will be left in the expired air. Or, in terms of percentages, the expired air of the rescuer will still have about 18 per cent oxygen concentration. This means that there will be available to the victim 1800 ml. of oxygen per minute. Assuming again that the victim also needs 300 ml. of oxygen per minute for metabolic purposes, there is more than a sufficient amount of oxygen in the 1800 ml. offered by the rescuer, and there is even a surplus of 1500 ml. or 15 per cent in relation to the minute volume. Thus it is easy to understand how a rescuer who may hyperventilate to some extent to supply 10,000 ml. of expired air may adequately supply the oxygen requirements of a person he is trying to resuscitate.

Carbon Dioxide Concentration. The next problem to be considered is the carbon dioxide concentration in the victim. Carbon dioxide is one of the chief products of metabolism and is eliminated mainly through the lungs. Respiratory depression will interfere with the elimination of carbon dioxide and result in a condition known as hypercapnia or respiratory acidosis. Since carbon dioxide is a waste product of metabolism, excessive amounts in the human body are deleterious. During apnea or insufficient ventilation, the increase in the carbon dioxide level in the human body first serves as a stimulant to many of the different organ systems. For instance, it stimulates the adrenal medulla to secrete glycogen into glucose. As the glycogen supply is exhausted, metabolic acidosis may develop. Carbon dioxide will cause a constriction of the peripheral blood vessels during the early phases of hypercapnia and cause a rise in blood pressure. Increased carbon dioxide may provoke convulsions. As the concentration of carbon dioxide increases, it becomes a depressant material and can cause anesthesia of the brain. Increased carbon dioxide may give rise to various irregularities of the heart rate and rhythm, and in excessive quantities, carbon dioxide will eventually result in death.

Expired air normally contains from 4 to 5 per cent carbon dioxide by volume. If this is introduced to an apneic subject who has already started to build up a high carbon dioxide level in his body, is this not unphysiological? Studies, however, of the alveolar air of the hyperventilating rescuer have showed the carbon dioxide

level to drop from the normal 4 to 5 per cent to 2 per cent. The unconscious apneic subjects subjected to expired air resuscitation also showed an actual diminution in the carbon dioxide concentration of their expired air. Further proof of this was reflected in the determination of carbon dioxide levels in the arterial blood. Studies by Elam and his group[1] definitely established that within the first few minutes after institution of expired air ventilation, the carbon dioxide tension in the arterial blood stream, which was quite high or elevated before resuscitation, very promptly dropped to normal or below normal levels. Other groups have confirmed these findings.

Rescuer's Ability to Maintain Prolonged Resuscitative Effort. The third factor to be considered in this method of resuscitation is the ability of the rescuer to continue this technique for long periods of time without fatiguing or overventilating himself and possibly losing consciousness. Studies were made whereby trained volunteers were made to ventilate different systems devised to test their ability to expend the effort necessary for prolonged mouth-to-mouth resuscitation, and no significant fatigue was seen in these volunteers. Even under unfavorable circumstances where resistance was introduced into the test models for mouth-to-mouth resuscitation, the volunteers did not experience fatigue and were able to perform successfully. Some of the volunteer rescuers were even required to exercise during the procedure and they still performed successfully without unduly fatiguing themselves.

At this point, the rate of ventilation becomes significant. It is common knowledge that if a person continuously breathes deep and fast, he very quickly becomes dizzy and may momentarily lose consciousness. This is due to the fact that as he overventilates, he eliminates carbon dioxide so fast that he goes into a state of respiratory alkalosis. Alkalosis frequently gives rise to dizziness, tingling sensations, and even unconsciousness. What should be the rate of resuscitation, that is, the number of times that the rescuer should ventilate the victim? One group recommended at least 20 times/minute with a tidal exchange of about 500 ml., or what would be equivalent to 10,000 ml./minute. Another group,[1, 2] which allowed the rescuer to set his own rate of inflation, showed that the rate was not very important provided the ventilation was sufficient so that the resulting inflation volumes and the alveolar gas concentrations in the victim were met satisfactorily to obtain a physiological condition. This group further recommended that for resuscitating adults by this method, the tidal volume should be at least 1000 ml. with a rate of from 12 to 20 inflations/minute. At this rate and volume, it is possible to continue ventilating the victim for periods of 30 minutes or more without dizziness affecting the rescuer.

In another study, the rescuer was deliberately made to hyperventilate maximally for at least two minutes with respiratory rates of about 50/minute and alveolar ventilation of more than 50 liters/minute. Abject dizziness became manifest in the rescuer within 30 to 60 seconds, and interestingly enough, alveolar carbon dioxide concentrations of the rescuer when determined were found to be between 2 and 5 per cent at the time the dizziness ensued. It was found, however, that dizziness did not occur in the rescuer if his alveolar carbon dioxide level stayed above 3 per cent. In 30 minutes of uninterrupted mouth-to-mouth breathing in one study,[3] at a rate of about 12 breaths/minute with tidal volumes between 1000 and 1500 ml., the victim's alveolar carbon dioxide remained normal or below normal, that is, between 4 and

FIG. 1. The rescuer's mouth is placed over the victim's mouth (and nose in children). The rescuer then blows with a smooth, steady action until the chest is observed to rise. Inset. The jaw is held forward between the thumb and fingers to pull the base of the tongue away from the posterior pharynx.

5 per cent and his arterial oxygen saturation remained between 97 and 100 per cent. On the other hand, the rescuer's alveolar carbon dioxide concentration was between 3 and 4 per cent. Thus, as far as rate is concerned, the recommended rates vary from 12 to 20 inflations/minute, but what is more important is that the tidal volume be at least 1000 ml./ventilation and no more than 1500 ml. In infants and children, of course, the volume of inflation must be less.

TECHNIQUE OF MOUTH-TO-MOUTH RESPIRATION

It is necessary to assure a clear airway: Any foreign body, secretions, or water in the oropharynx and possibly the trachea should be removed with the finger, or by turning the victim on his stomach, then inserting a finger into the mouth, pulling the tongue forward, and tapping the back gently. The base of the tongue must be kept from falling back against the posterior pharynx so that obstruction of the airway is avoided. This can be done by forcing the jaw to assume the prognathous or the "sniffing air" position, which may be accomplished in two ways: by holding the

FIG. 2. The rescuer listens for the onrush of exhaled air from the victim.

FIG. 3. Gentle steady pressure on the abdomen of children prevents distention of the stomach.

lower jaw between the thumb and forefinger and pulling it forward (fig. 1, inset) or by forcing the lower jaw forward by pressing at the angle of the jaws with either the forefingers or the middle fingers.

The rescuer should place his mouth over the mouth of the adult victim (figure 1) or the mouth and nose of the child victim and then breathe with a smooth, steady action until the chest is observed to rise. The rescuer should then remove his mouth from the victim's mouth, turn his head partly to the side, and listen or feel with his turned face for the onrush of the victim's exhaled air (fig. 2). In the child, it is important to apply a steady gentle pressure with one hand on the abdominal wall (fig. 3) to prevent distention of the stomach. Abdominal distention, in the child particularly, can interfere with respiration and may occasionally give rise to reflexes that are deleterious to the heart.

The artificial respiration should be continued at the rate of about 20 respirations/minute with a tidal volume of at least 1000 ml. in the adult, which is difficult to measure under the circumstances but may easily be gauged by the fact that the chest is rising, an assurance at least of effective ventilation.

FIG. 4. Mouth-to-mask method.

FIG. 5. Mouth-to-airway method.

VARIATIONS OF THE MOUTH-TO-MOUTH METHOD OF RESUSCITATION

Elam and his group, of course, have advocated the use of a mask (fig. 4), so that the rescuer blows into the mask instead of directly into the victim's mouth.

Another device, developed by Lee, Tarrow, and Ward[4] of the U. S. Air Force, is nothing more than a mask with extended tubing, which has a valve for the victim to exhale through after being ventilated by the rescuer. It is called the Venti-breather or Resuscitator. Studies of oxygen concentrations and carbon dioxide concentrations during actual use of the unit in volunteers showed its effectiveness for the purpose in the adequate maintenance of normal oxygen and carbon dioxide levels in the arterial blood.

Safar and his group[3] have introduced the use of the Guedel airway (fig. 5). They connected two rubber airways together, a small one and a large one, and employed this as a means of breathing into the victim. The airway has a twofold purpose: it serves to prevent the tongue from falling back against the posterior pharynx, and it serves as a tube by means of which the rescuer breathes into the victim. One of the problems with this method, of course, is the leak around the airway, which may prevent an effective resuscitation of the victim. However, recent modifications show a wide enough flange that more or less seals the lips and prevents leakage around the airway. The joint airways, of course, are in two sizes—a small one for children and a large one for adults; thus the device serves another dual purpose in that one end may be employed for adults and the other end for children.

CONCLUSIONS

In conclusion we believe that of all the methods of artificial respiration studied so far, the expired air ventilation is most convenient. It is also an effective method for resuscitation.

The two most important considerations in performing expired air ventilation are: to maintain a clear and patent airway and to supply a sufficient volume of air to the

patient so that his oxygen requirements are satisfied and his excess carbon dioxide is eliminated.

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6th International Congress of Internal Medicine

The 6th International Congress of Internal Medicine will be held Aug. 24–27 in Basel, Switzerland. The Congress has been organized by the International Society of Internal Medicine (president, Sir Russell Brain, F.A.C.P. Hon., London).

Principal subjects of the Congress will be: pathogenesis and therapy of edema and enzymic regulations in the clinic. There will be panels on interstitial nephritis, nephrosis, diuretics, diagnostic value of the enzymes, therapeutic indications of the enzymes, serology in rheumatic diseases, instruction in internal medicine. There will also be lectures on subjects of free choice. Seventy leading internists from all over the world will take part in the main scientific program by reading their papers or joining in the panel discussions.

Official languages of the Congress will be German, French, and English, with simultaneous translation for the principal lectures. Further information may be obtained from the secretary of the 6th International Congress of Internal Medicine, Steinentorstrasse 13, Basel 10, Switzerland.

Management of Chronic Eczematoid Dermatitis of the Hands

A Treatment Program with Iodochlorhydroxyquin-Hydrocortisone Cream

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Chronic eczematoid dermatitis is a complex clinical condition that may result from a variety of etiological sources. Attempts at classification according to etiology, location of the lesion, etc., have been made. The condition, however, does not readily lend itself to categorization since no single satisfactory criterion of differentiation is possible.

This condition is important to the physician by virtue of its prevalence and the marked discomfort and disability it can cause. To the dermatologist and practitioner, it presents a therapeutic challenge because the intense irritation of the skin must be skillfully managed to prevent aggravation and frequent exacerbation of the lesions.

Clinically, the skin lesions are often typical and ordinarily are not difficult to distinguish from lesions of other skin disorders. Erythema and swelling of the skin appears very early in the evolution of the typical lesion. Oozing and vesiculation are common with resulting crust formation and scaling. If the lesion persists, there is a tendency to hyperpigmentation of the affected skin with lichenification. Scratch marks and other evidence of repeated excoriation are quite common.

Microscopically, the picture of chronic eczematoid dermatitis is one of dermal edema and vascular dilatation. The edema is both intercellular and intracellular and culminates in vesicle formation within the cells of the epidermis. This causes the skin to feel tough and infiltrated and will eventually produce oozing and resulting crust formation. Quite early there is a perivascular cuffing with inflammatory cells consisting largely of lymphocytes. If the lesion persists, the epidermis thickens and there is a tendency to capillary proliferation.

This study was an attempt to evaluate the effect of a dermatological cream, iodochlorhydroxyquin-hydrocortisone (Vioform-hydrocortisone*), in the management of chronic eczematoid dermatitis of the hands. Iodochlorhydroxyquin is a nonirritating organic compound that contains approximately 41 per cent iodine. It is fungicidal and bactericidal and has proved itself a valuable adjuvant in the treatment of various skin disorders. Hydrocortisone is an anti-inflammatory corticosteroidal compound. The particular formulation employed contains 3 per cent iodochlorhydroxyquin and 1 per cent hydrocortisone in a water-washable base.

Our patient group consisted of 44 patients with chronic eczematoid dermatitis of the hands from varying etiology. Four patients were less than 20 years old, 35 were

* The trade name of Ciba Pharmaceutical Products Inc. for iodochlorhydroxyquin-hydrocortisone is Vioform hydrocortisone.

20 to 50 years old, and 5 were more than 50. There were 5 male patients and 39 female patients.

ETIOLOGY

Etiological diagnoses were based on clinical impressions supported by the patient's history and other physical findings. The contact factor was discovered and eliminated in 3 of the patients with contact dermatitis.

Nine patients had atopic dermatitis; 6, contact dermatitis; 4, id reaction from active tinea pedis; 3, pyoderma; 22, "housewife's" eczema from detergents and/or monilial infection.

INSTRUCTIONS TO THE PATIENTS

The patients were instructed to rub a small amount of the cream into the affected areas of the hands on arising and at bedtime. They were also told to use the cream after washing or wetting the hands during the day.

When the skin lesions had completely cleared, the patients were told to apply the iodochlorhydroxyquin-hydrocortisone cream only at bedtime or after deep, prolonged hot water exposure. This routine was continued for two months after apparent clinical cure. The patients were advised not to use rubber gloves and to avoid deep hot water contact as much as possible. Housewives were instructed to use hand mops for washing dishes.

ADDITIONAL THERAPY

Colorless aqueous benzalkonium in a 1:1000 solution was used twice daily as a nonirritating skin cleanser by the 22 patients with housewife's eczema. Antihistamines were administered to 3 patients with id reactions who still had intense itching 10 days after onset of therapy with iodochlorhydroxyquin-hydrocortisone cream. Burow's solution (1:40) soaks, 20 minutes twice daily, were used for 72 hours by 3 patients with acute weeping lesions.

RESULTS

Forty-four patients were treated and observed after 2, 8, 16, and 24 weeks of therapy. The patients' responses to the medication were graded as improved or cleared.

At two weeks, all the patients under this treatment regimen showed improvement except 2 patients who developed irritation of the lesions from the medication. This represents an incidence of improvement of 95.5 per cent. The irritation in these 2 cases was felt to represent an iodine reaction; however, the only patch test with iodochlorhydroxyquin was negative. The other patient was not tested.

At eight weeks, the remaining group of 42 patients was again evaluated. One patient showed irritation to the medication, which was discontinued. All of the remaining 41 patients (93.2 per cent of the total series) continued to improve.

At 16 weeks, of the remaining 41 patients in the study, 39 or 88.6 per cent of the

total series showed complete clearance of lesions. Two patients or 4.5 per cent of the total series showed an acute relapse of lesions.

Observation of the group of 41 patients who continued therapy according to instructions for 24 weeks showed complete clearance of lesions in 29 cases (65.9 per cent of the total series); 9 patients (20.5 per cent) of the group continued to show slight occasional flare-ups of the lesions, which responded readily to iodochlorhydroxyquin-hydrocortisone cream applied twice daily. Three patients (6.8 per cent) showed relapses of the condition and were not significantly benefited by the treatment.

SUMMARY

In the treatment of eczematoid dermatitis of the hands, iodochlorhydroxyquin-hydrocortisone cream produced improvement in 95.5 per cent of the patients at the end of two weeks. At the end of eight weeks, 93.2 per cent of the patients continued to improve with this medication. In none, however, had complete clearing taken place. By the end of 16 weeks, the lesions had completely cleared in 88.6 per cent. Since patients were prone to neglect therapy once lesions were clear, they were instructed to use iodochlorhydroxyquin-hydrocortisone once a day and after long immersion of the hands in hot water. On examination at 24 weeks, 65.9 per cent showed completely clear skin. In the group studied, 20.5 per cent reported occasional eczematous flare-ups, which were readily cleared using iodochlorhydroxyquin-hydrocortisone cream twice daily. In 6.8 per cent, there was a complete relapse by the twenty-fourth week of the study.

These results indicate the necessity for long-continued, intensive therapy in a condition so persistent and subject to relapse as eczematoid dermatitis of the hands.

CONCLUSION

Iodochlorhydroxyquin-hydrocortisone was found to be an aesthetically acceptable dermatological preparation with a high degree of effectiveness in the treatment of chronic eczematoid dermatitis of the hands.

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Bowel Rehabilitation in the Chronically Constipated Patient

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The treatment of chronic constipation ideally must not be confined merely to continued pharmacological irritants to relieve the symptomatic manifestations, but should attempt to correct the basic physiological fault by stimulating actual rehabilitation of the normal process of evacuation. The rational medical management of constipation therefore requires the use of an agent that not only can produce a predictable laxative response but that also will restore neuromuscular sensitivity and so reactivate the reflex mechanism of evacuation. Common experience indicates that the usual laxatives fail to accomplish this goal; moreover, continued use leads to dependence on them.

It has been of great interest, therefore, to note the many statements that a standardized and purified derivative of senna* acts in a manner indistinguishable from the normal intrinsic mechanism of bowel function and, in clinical use, has led to the resumption of normal bowel activity.[1–3] We were further stimulated by the recent studies of Tirsch and Rosenfeld[4] indicating the successful management, with this preparation, of intractable constipation in severely ill neurological patients. We were therefore led to determine whether the administration of this agent to patients who had obtained only temporary relief from other laxatives might not only afford the desired symptomatic relief but also result in resumption of normal bowel rhythm without further use of the agent.

METHODS AND MATERIALS

The 25 patients in this study were selected from office practice. Their ages ranged from 36 to 74 years, with an average age of 56. All patients suffered from intractable constipation of long duration. Prior to the study, each patient had been using various laxatives, including milk of magnesia, mineral oil, cascara, a phenolphthalein proprietary preparation, citrate of magnesia, and enemas. None of these preparations afforded more than temporary relief.

Constipation in these 25 patients was associated with the following conditions: anxiety 3, coronary thrombosis 4, malignant process 4, hypothyroidism 2, obesity 3, hemorrhoids 3, postcholecystectomy 1, colitis 1, gastritis 1, duodenal diverticulum 1, duodenal ulcer 1, hypocholesteremia 1.

The starting dosage of the standardized senna preparation was 1 level teaspoonful nightly for a period of two to six months. When necessary, the dose was increased by half teaspoonfuls until maximum effectiveness was established. When considered necessary, dietary changes were advised to provide adequate bulk. This regimen was

* The trade name of The Purdue Frederick Co. for a standardized senna preparation is Senokot.

continued for one month, at which time the dosage was gradually reduced by half teaspoonful measurements, unless constipation recurred.

Criteria for judging results were as follows: excellent, when bowel rehabilitation was established without any further need for the senna preparation or when only occasional use was necessary; good, when a weekly dose was required to aid evacuation; poor, when little or no improvement was shown.

RESULTS

Excellent results were achieved with 17 of the 25 patients. Of these 17 patients, 10 reported complete bowel rehabilitation after the senna preparation was discontinued. In follow-up studies at six-month intervals for two years, these patients showed normal bowel function. The remaining 7 patients in this group required an occasional dose for normal function. In 6 patients there were good results; a weekly dose was required for continued regularity. Of the 25 patients, only 2 failed to show any improvement. One of these discontinued therapy early in the study because of an intolerance to cocoa, one of the ingredients of the preparation.

Twenty-two patients were able to reduce or eliminate dosage within a five-month period, whereas the remaining 2 patients continued treatment for an additional month.

Other than mild cramps or occasional griping experienced by 4 patients, there were no side effects. One of these 4 no longer complained after the first day and a second patient was free of mild cramps after the third day. The remaining 2 patients had occasional mild cramps during the course of treatment but not troublesome enough to interfere with therapy.

DISCUSSION

The primary aim in constipation therapy is the restoration of normal bowel function through gradually re-established neuromuscular stimulation. Ingegno[5] indicated that the "final common path for stimuli to affect the colon resides in the autonomic nervous system and the neuroeffector junction in the bowel." Autonomic imbalance invariably involves all or part of the colon and creates chronic retardation of large bowel peristaltic activity. Re-education of the neural reflex patterns mediated through Auerbach's plexus allows normal motility to be established once again and eliminates the need for continued cathartic stimulation in many cases.

Pharmacodynamically, the senna glycosides are absorbed into the blood stream from the small intestine, without effecting the motility of the stomach or small intestine, and are excreted into the large bowel, where they are converted by enzymatic action into glucose and aglycone. The latter acts specifically on Auerbach's plexus.[6, 7] The ensuing peristaltic movement is thus produced by innervation of neurogenic and muscular action rather than by irritation of the mucosa. Abrahams[8] defined this neuromuscular mediation through Auerbach's plexus as a "reproduction of the physiological process of normal defecation. . . ." In a more recent observation Abrahams[9] stated that ". . . the standardized preparation of senna, as a selective

neuromuscular stimulant to the large bowel, is the safest and most physiological laxative of today."

Constipation cannot be regarded merely as an insignificant disorder of colonic motility. Whether it is caused by dysfunction of the neuromuscular mechanism or voluntary inhibition arising out of fissure, hemorrhoids, or environmental retardation, chronicity ultimately leads to muscular weakness and what might be termed insufficiency. Prolonged reliance on cathartics often results in permanent loss of bowel tone, with atonic distention. In more serious cases the continued use of these cathartics can sometimes lead to severe impaction and acute obstruction. The proper treatment of chronic constipation can in many instances be lifesaving, particularly in patients with cardiovascular diseases where straining at the stool may result in death from alterations in vascular dynamics.[10, 11]

SUMMARY AND CONCLUSIONS

1. A standardized senna preparation was evaluated in treatment of 25 patients whose histories showed chronic constipation of at least five years' duration.

2. Of this series, 17 patients reported excellent results. Bowel rehabilitation without further need for laxatives was established in 10 of these 17 patients. The remaining 7 patients in this group of 17 had need for an occasional dose of this preparation for maintenance of bowel tone. Six of the 25 showed good results and were continued on a weekly regimen of the preparation. Failure was reported in 2 patients, one of whom was intolerant to cocoa. Five patients complained of transient and occasional mild cramps and griping, none of these severe enough to warrant discontinuing treatment.

3. The results indicate that this senna preparation is an effective bowel corrective capable of establishing excellent control of constipation in the majority of patients, irrespective of the severity or duration of the disorder. In 40 per cent of the patients full establishment of normal bowel function was obtained without a maintenance dosage.

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Organization and Function of a Psychiatric Consultation Service

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Although the high incidence of emotional disorders in medical and surgical patients has been recognized for many years, the full use of the psychiatrist in a general hospital is not usually achieved. In many instances, a psychiatric consultation is still regarded with more misgivings than is an arduous diagnostic procedure or an exploratory operation. As a result, the psychiatrist's participation may be requested only for the management of patients whose mental disorder is unmistakable or whose care the physician is eager to relinquish.

In an effort to provide more comprehensive psychiatric participation in the care of hospitalized patients, a psychiatric consultation service has been developed during the past four years at the Massachusetts General Hospital, a teaching institution of the Harvard Medical School. Under the first chief of the psychiatric service, Dr. Stanley Cobb,[1] this hospital was among the earliest to establish a unit for the study and treatment of psychoneurotic and psychosomatic disorders. Dr. Erich Lindemann,[2] the present chief, has been a pioneer in the study of the effect of crisis on the individual patient in the setting of interpersonal relationships. The natural consequence of this and other work, especially that concerning the physician-patient relationship[3] and the formulation of conflict,[4] has been to apply this information to the study and care of patients who are not primarily suffering from psychiatric disorders. The results have been a fruitful, mutually beneficial experience to the psychiatrists and to the specialists in other fields. Since our experience may provide other hospitals with an incentive to initiate similar services, we are reporting how the organization and function of a consultation service may further the aims of patient care, research, and teaching.

DEVELOPMENT

With rare exceptions, the bulk of psychiatric consultations prior to the organization of the service consisted of psychoses, deliria, and disposition problems. There were, of course, many psychosomatic projects in which medical patients were studied from the psychiatric viewpoint, but these were planned activities and not a part of the regular treatment program. As a rule, when the project terminated, there was no indication that interest in psychiatric problems continued. The therapeutic consultation was a rare occurrence. For the nonpsychiatrist, psychiatric issues had largely academic, rather than practical, significance. The gap between the pious platitudes of a physician who stressed the importance of a holistic approach to patients and his actual consultation requests to the psychiatrist was often incongru-

ously wide. In return, the psychiatric consultation service to other departments tended to become the peripheral concern of the residents to whom it was assigned, among their other more pressing duties.

In 1956, when the consultation service began systematic work, the personnel consisted of the two authors, who collaborated in providing psychiatric service that would be appropriate to the problems of the internist, surgeon, or other specialists. This meant that in order to make a practical contribution, the entire structure of the consultation service had to be geared to the urgency of medical or surgical situations, rather than to the somewhat deliberate, even leisurely, type of evaluation that the psychiatrist usually employs.

Consultation requests were answered promptly, at once in some cases, but never more than 24 hours later. However, in order to combine accuracy with mere alacrity, the consultation staff held frequent conferences. The senior consultant and the junior administrator developed a systematic method of evaluation and formulation, from which a rational plan of management could be proposed. In every case, scrupulous attention was given to the reason for which assistance had been sought. The physician's explicit reason for consultation more often provided information about the relation between physician and patient than it did about the psychopathology of the patient himself. For example, if a patient insists on signing out against advice, it may indicate a serious defect in reality testing, particularly if a mandatory operation is involved. However, a patient may demand discharge because of a misunderstanding with his physician or with some nonprofessional member of the staff or because of an attitude of pseudoindependence that the patient may adopt in the face of a threat. Careful attention to the precipitating circumstances of many consultation requests often indicated that there had been a disruption in the physician-patient relationship, which could be rectified readily.

In every instance, the psychiatric reports to the physicians were practical. The findings were expressed in familiar clinical language rather than in specialized psychiatric terminology. However interesting from a psychodynamic viewpoint, irrelevant or extraneous material was omitted. Whenever possible, the consultant made a point of discussing the problem personally with the physicians in charge. In some cases, he spoke with the nurses or attendants in order to obtain accurate information about the patient's behavior and attitude. Finally, the psychiatrist did not rest with simply stating the psychological problems or making vague recommendations to somewhat dubious medical and surgical house officers. He outlined a therapeutic program of management and was the active participant in implementing it. This naturally required more than a single visit. In some instances, the patient was followed daily by the psychiatrist for the balance of his hospital stay.

Active participation by the psychiatrist had important consequences. At first, psychiatric referrals consisted largely of acute psychotic disorders or problems of disposition or commitment. However, by taking over in such prosaic matters, by speaking with relatives or with social workers, the psychiatrist, by his greater facility in dealing with interpersonal problems, freed the ward physicians from what is, to them, frequently an irksome task. Moreover, the psychiatrist's sustained interest, activity, and frequent success in managing certain difficult patients led to

a gradual increase in the number of requests for his services. With it came a wider variety of patients, some of whom would not usually be referred to a psychiatrist. This included patients who were disruptive influences on the ward, patients who were unduly dependent or negativistic, patients who were anxious, depressed, or paranoid prior to and after surgery, as well as many with diagnostic problems that involved conversion reactions, chronic invalidism, failure to respond to therapy, and other difficulties.

THE THERAPEUTIC CONSULTATION

The exigencies of formulating and implementing a management program necessitated a change in the conventional technique of psychiatric evaluation. The unique contribution that gradually evolved was that of the *therapeutic consultation*. The beneficial effect of brief contact with patients for limited objectives is familiar to general hospital psychiatrists. Since most psychiatric consultations, except those in which a psychiatric opinion is merely "window dressing" for a well-studied case, are at least as urgent as the medical or surgical illness from which the patient suffers, the entire relationship with the patient had to be reduced to its most important essentials. There were, it seemed, four phases to the work of therapeutic consultation: rapid evaluation, with special attention to the personal factors and the reason for consultation; psychodynamic formulation[4] of the major conflict, predominant emotional patterns, ego functions, and object relationships; rational programming of a therapeutic intervention, based on the formulation; and active implementation by the psychiatrist himself.

Although the therapeutic consultation clearly aided the physician in his work and helped to maintain the psychic equilibrium of the patient, it was apparent that when the patient left the hospital, problems and conflicts would frequently recur. The psychiatrist fully recognized that in some instances he had provided only a temporary measure, designed to help the patient through a difficult crisis. When feasible, recommendations for posthospital psychotherapy were offered. However, many patients did not need subsequent psychiatric referral. Ordinarily, according to all reports, they had functioned well within normal limits from their own and the community's viewpoint. In other patients, there was clear evidence that posthospital psychotherapy was indicated, but the patients refused this help. The psychiatrists had to remind themselves that the primary objective of consultation therapy is not to treat a primary psychiatric disorder, but to relieve those factors that complicate convalescence in a medical or surgical illness.

The combination of streamlined evaluation, brief contact, and limited aims may suggest that the therapeutic consultation consisted merely of nonspecific supportive measures. This does not accord with the facts, as reference to our other publications will confirm.[4, 5] Intervention, based on a specific and firm physician-patient relationship and on a cogent formulation of issues, depends fully as much on the physician's psychodynamic insight and understanding as do more protracted therapies in which interpretation is the medium of communication. The great variety of consultation problems challenges both the physician's understanding and his versatility.

USE OF CONSULTATION MATERIAL IN CLINICAL RESEARCH

One of the most important aspects of the therapeutic consultation was a change in emphasis from disease orientation, in which the patient is an illustration of pathological processes, to patient orientation, in which individual personal motivation and impaired ego capacity influence the adaptation to illness. The predominant clinical problem for which consultation was requested became the focal point of investigation, not merely as a symptom of disease or as an indication of the physician-patient relationship, but more as an expression of crisis or conflict with which the patient, as a human being at that instant in time, was confronted. Conventional classification of psychiatric findings according to disturbances of thought, affect, and behavior was insufficient. The personal factors had to be accounted for, quite apart from the primary disease or operation. This was accomplished by distinguishing between impersonal, intrapersonal, and interpersonal factors. The impact of the impersonal consisted of the crisis that imposed itself on the patient, often like a stroke of fate. The intrapersonal factor was the conflict that the illness had evoked, and included the various anticipations, wishes, fear, dreads, and hopes that a threatened incapacity may carry. Finally, the interpersonal factor consisted of the relationships that the patient had with his world of people and things, in his family and occupation, and that contributed to his unique pattern of reality testing.

The patient-oriented viewpoint, coupled with psychodynamic formulation of the factors associated with crisis, conflict, and reality testing, provided both a basis for therapeutic intervention and areas for further investigation. Indeed, many more problems emerged from this viewpoint than there were resources to study them. For example, a study of patients with "black patch delirium"[5] was undertaken, by postulating that reality testing depends both on perceptual information and on sustained interpersonal relationships. In trying to deal adequately with the crisis imposed by the operation and occlusion of vision, it was surmised that conflicts would be evoked by the impaired ego capacity and defective reality testing. As a result, a specific type of therapeutic intervention was devised, in which the physician unambiguously established himself as a knowledgeable ally and punctiliously supplied the patient with supplementary, nonvisual information about the operation, his surroundings, and his hospital course. In addition, because the ego capacity was threatened at this instant in the patient's life, the psychiatrist concentrated his attention on that period in the past when ego capacity had operated most efficiently and with greatest satisfaction to the patient. The therapeutic response was prompt; the hospital course was less stormy and the convalescence was far smoother than had been anticipated.

These findings suggested further investigation into the impersonal effect of other types of operation. In turn, this led to study of various kinds of psychiatric syndromes associated with surgery,[5] and, from here, still other issues presented themselves. The important point is not that research is an inherent function of a psychiatric consultation service; this is an obvious inference. Rather, it became clear that a consultation service need not derogate itself because its contact with patients is brief and the information limited. Instead of following the usual practice of first

setting up a program for investigation, ordinary consultation activity is so replete with rich material that problems have only to be extracted.

Analyzing the content of consultations for research possibilities requires regular review of the records. This brings together many cases that may have been recorded at different times. In their consultation conferences, the psychiatrists organize data and systematically question the hypotheses that underlie their treatment of patients.

TEACHING FUNCTION OF THE CONSULTATION SERVICE

The activities of the consultation service were enhanced when it became a regular assignment for younger psychiatrists in advanced stages of their training. The skills involved in rapid evaluation and practical intervention provided the psychiatrist with a useful counterpart to his theoretical knowledge and an adjunct to his experience with psychiatric patients. The usual practice of merely adding consultation duties to other duties has been recognized as unsatisfactory. At least half of a physician's time for the better part of a year is needed in order to develop facility in this branch of general hospital psychiatry. Training in consultation psychiatry consists of individual supervision in formulating and implementing therapeutic interventions and attendance at consultation conferences and rounds of the entire department. In addition to regular consultations, the psychiatrist in training is assigned a special research problem, which is part of larger, continuing projects. Supervision in his investigative studies is also provided. The research problems are so designed that the young psychiatrist can reasonably be expected to complete his investigation during his period of duty. There are two teaching aims: to train the psychiatrist to see the patient as he resembles other patients with similar medical or surgical disorders and to see the patient as he is, or would be, without the illness.

SUMMARY

The organization, development, and function of a psychiatric consultation service in a general hospital have been described. Its chief objective is to improve the quality of patient care from the psychiatric viewpoint. This has been brought about by developing the therapeutic consultation, a planned intervention based on rapid evaluation, psychodynamic formulation, rational management, and active implementation by the psychiatrist himself. The therapeutic consultation at times requires considerable variation from conventional psychiatric techniques of interviewing and treatment. This has made consultation duties a valuable addition to training of psychiatrists.

The general theoretical approach is patient oriented, rather than disease oriented. Particular attention to impersonal, intrapersonal, and interpersonal factors has provided significant information with regard to crisis, conflict, and reality testing. The patient-centered viewpoint entails many unique research possibilities, some of which are outlined.

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A Decade of Chemotherapeutic Control of Acute Leukemia

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The advances made in the management of acute leukemia through chemotherapy during the last decade have been remarkable. In 1950 Gunz wrote: "The treatment of acute leukemia is distressingly ineffective. In hardly any other disease can so little be done to ease the patient's suffering, let alone bring about any clinical improvement." Less than a decade later Murphy, in reviewing advances in the therapy of leukemia and lymphomas in children, wrote: "Drug-induced remissions in the acute leukemias of childhood have rightly been called one of the most remarkable phenomena of modern medicine."

A consideration of the scores of review articles and hundreds of original clinical reports in the control of acute leukemia through chemotherapy gives a much more confused picture than that drawn by these opening statements. Reviewers differ sharply on the relative merits of the several chemotherapeutic agents, and the clinical reports often present conflicting and contradictory data. Since much of the original literature is found in foreign publications—60 per cent of the references of the complete bibliography of this paper are from medical centers outside the continental limits of the United States—an attempt has been made in this study to cover the reviews on the three most frequently employed chemotherapeutic agents and to cover in more detail the clinical reports on other chemicals used in the management of acute leukemia.

Folic acid antagonists, adrenal steroids, and 6-mercaptopurine have dominated the current management of acute leukemia. It was noted in a recent study[29] that 85 per cent of all patients with acute leukemia were treated with these three antileukemic agents. The most frequently used chemotherapeutic agents in the remaining 15 per cent were nitrogen mustards, radioactive isotopes, antibiotics, triethylene melamine, colchicines, vitamins, urethan, busulfan, and a score of other miscellaneous chemicals. These latter serve as an important link in the screening of agents that may prove successful in the future control of acute leukemia.

FOLIC ACID ANTAGONISTS, ADRENAL STEROIDS, AND 6-MERCAPTOPURINE

A number of reviews have appeared on the management of acute leukemia with folic acid antagonists, adrenal steroids, and 6-mercaptopurine. In 1956 the A.M.A. Council Report on the Current Status of Therapy of Leukemia[1] reported that the most satisfactory therapeutic results were obtained in acute lymphocytic and acute granulocytic leukemia with antimetabolites and steroid hormones, while 6-mercaptopurine gave good management of acute monocytic leukemia. Burchenal[10] favored steroids and antimetabolites: he listed survivals in untreated cases of acute

leukemia as averaging only four months, with patients on nitrogen mustard averaging five months' survival, those on folic acid antagonists or adrenal steroids, or both, averaging 8.9 months' survival, and patients on a combination of folic acid antagonists, adrenal hormones, purine antagonists, and azaserine averaging 12.4 months' survival. In another review in 1954 Burchenal[9] favored sequential therapy to combination therapy in acute leukemia in children. He cited only 5 per cent survivals of one year or longer in 218 untreated patients, with 29 per cent survivals among 154 children on cortisone and folic acid antagonists and 52 per cent survivals in 52 children on folic acid antagonists, cortisone, and 6-mercaptopurine. And in 1958 Burchenal[11] evaluated methotrexate, amethopterin, as the best of the folic acid antagonists.

Best and Limarzl[5] have estimated that 30 per cent of all leukemias in adults are acute or subacute and that two thirds of these are acute granulocytic. They recommended steroid hormones and 6-mercaptopurine for therapy in adults. They compiled a table on acute leukemia in children, which showed 60 per cent remissions with folic acid antagonists for a median time of six months, 40 to 60 per cent remissions with 6-mercaptopurine for two months, 50 per cent remissions with steroids for one month, and 80 to 90 per cent response on a combination of ACTH and folic acid antagonists for 1 to 24 months. Ellison[12, 13] in two studies favored folic acid antagonists, steroid hormones, and antipurines in acute leukemia. He estimated that 5 to 10 per cent of all adults responded to folic acid antagonists, while in children the percentages ranged from 30 to 50. He also used 6-mercaptopurine for treatment of adults with acute leukemia. Wilson et al recommended corticosteroids, 6-mercaptopurine, and folic acid antagonist therapy for children with acute leukemia and large dosages of corticosteroids and 6-mercaptopurine for adults. Of the 2424 cases he selected from the literature, 16.7 per cent of patients had acute lymphocytic leukemia, 16.4 per cent acute myelocytic, and 7.0 per cent acute monocytic leukemia. Bove and Emerson judged folic acid antagonists best for acute leukemia in children and these antagonists and 6-mercaptopurine best in adults. Brimi[7] estimated folic acid antagonists and steroid hormones to be effective and preferable in the control of acute lymphoid leukemia, while 6-mercaptopurine was moderately effective, but busulfan and urethan were ineffective, and radiophosphorus, triethylene melamine, and nitrogen mustard actually hastened the downhill course of the disease. In myeloblastic leukemia he listed folic acid antagonists as effective, 6-mercaptopurine as moderately effective, busulfan and urethan as ineffective, and steroids, nitrogen mustard, and triethylene melamine as contraindicated. Chatterjea favored folic acid antagonists, steroids, and purine antagonists, while he considered radiation therapy, nitrogen mustard, and triethylene melamine useless, if not harmful, in acute leukemia.

Erf[15] listed cortisone as his first choice in the therapy of acute lymphocytic leukemia, with aminopterin as second choice and ACTH as third. In acute myelocytic leukemia he preferred treatment with lymphokentric acid, with urethan as his second choice and brewers' yeast as third. For acute monocytic leukemia he ranked yeast as the agent of first choice, cortisone as second, and ACTH as third. Singh considered that cortisone showed its maximum value in the treatment of acute lymphocytic leukemia

and that it was probably contraindicated in acute myelocytic and monocytic leukemias. Tivey in 1952 concluded that there were not sufficient data in the 428 cases he compiled of acute leukemia in children to evaluate the effects of ACTH, cortisone, and folic acid antagonists. Two years later he observed 10 per cent spontaneous remissions in untreated patients with acute leukemia and 50 per cent in those given adrenal steroids.

Amado Ledo listed aminopterin as the agent of choice in the control of acute and subacute leukemia and amethopterin and steroid hormones as second choice, with cortisone and 6-mercaptopurine and 6-chloropurine as third choice. Ariens listed cortisone as his first choice in acute lymphocytic leukemia and aminopterin as first in acute myelocytic leukemia; cortisone and 6-mercaptopurine were his second choice in myeloid leukemia and aminopterin and 6-mercaptopurine his second in acute lymphoid leukemia. Bernard favored folic acid antagonists and 6-mercaptopurine as the two agents of first choice in acute leukemia. Bethell[6] assigned folic acid antagonists first place in the treatment of acute leukemia, followed by adrenal steroids as the chemicals of second choice. He stated that, in the opinion of most hematologists, radiation therapy was playing a secondary role to that of drugs in the management of both acute and chronic leukemias. Fountain[18] preferred the use of 6-mercaptopurine at first in children with acute leukemia, followed by folic acid antagonists and cortisone; in severe cases, however, adrenal steroids were the first line of treatment because of their rapid action. He prescribed 6-mercaptopurine first for adults also, and in emergency cases he resorted to ACTH or cortisone. Green came to similar conclusions. Fowler and Jolly recommended folic acid antagonists and purine antagonists for all types of acute leukemia. Galton favored folic acid antagonists in acute leukemia in children and nitrogen mustard, CB1348, for adults. Arini[2] reported some good remissions with a combination of 6-mercaptopurine and cortisone in 101 cases of acute leukemia; he also observed good remissions in 15 patients on methotrexate and in therapy with a combination of 6-mercaptopurine and radiophosphorus. Karnofsky[20] concluded that 50 to 80 per cent remissions could be induced in children for one year by treatment of acute leukemia with folic acid antagonists, purine antagonists, and adrenal steroids. A panel on "Newer Drugs in Therapy of Malignant Diseases" evaluated folic acid antagonists as effective in 30 to 50 per cent of children with acute leukemia. Marlow and Bartlett listed folic acid antagonists and adrenal steroids as the preferred agents in acute leukemia, but they considered the treatment of all other types as unsatisfactory. Other investigators recommending folic acid antagonists, purine antagonists, and adrenal steroids in acute leukemia include Davis, Farber, Schulten and Pribilla, Sulli, and Wintrobe et al.[30]

A detailed discussion of the more than 400 clinical reports presented in these reviews on the use of folic acid antagonists, adrenal steroids, and 6-mercaptopurine in the management of acute leukemia is beyond the scope of this paper, but recent surveys[25–29] permit the tabulation of the data in table I.

The terms "good" and "fair" remissions in table I point up one of the serious limitations in the evaluation of chemotherapy of acute leukemia. The absence of objective standards in determining the degree of response to the several agents[27, 28]

has led to the confusion apparent in the reviews on the subject. Criteria have been proposed for a more scientific evaluation of the results in acute leukemia, but since clinical reports are prepared for publication by hundreds of investigators in many parts of the world, it is not possible at present to differentiate the findings in more precise terms than the qualitative "good" and "fair." The good responses range from complete hematological and clinical remissions for prolonged periods to a satisfactory hematological or clinical response for several months, while the term "fair" is reserved for those cases that show some definite improvement clinically or hematologically for shorter periods.

Another shortcoming of the extensive literature apparent in table I is that a number of published investigations fail to give the number of patients treated and the number responding.[25] Publications that do not indicate the number of patients treated range from 13 for adrenal steroids, to nine for folic acid antagonists, eight for miscellaneous agents, and five for antibiotic therapy. Reports omitting the number of patients responding range from 20 for folic acid antagonists, to 16 for steroids, to 10 for miscellaneous agents.

NITROGEN MUSTARDS

Nitrogen mustards rank fourth among the most frequently used chemotherapeutic agents in the management of acute leukemia. However, the effectiveness of the newer nitrogen mustards (nitromin, chlorambucil, degranol, etc.) in the treatment of chronic myeloid and lymphoid leukemia, Hodgkin's disease, and related malignant disorders has not been duplicated in acute leukemia.

Reviews. Brimi,[7] Greenstein et al, and Wintrobe et al[30] listed nitrogen mustard as contraindicated in acute leukemia. Chatterjea concluded that these drugs were useless, if not harmful, and a panel on "Newer Drugs in Therapy of Malignant Diseases" warned of the dangers associated with nitrogen mustard therapy of acute leukemia. Burchenal[10] estimated that the nitrogen mustards prolonged the lives of patients: he gave four months as the mean survival time of untreated patients and five months for those on nitrogen mustards. Galton judged CB1348 to be effective in acute leukemia.

Clinical Reports. Almost one half of the clinical reports on the use of nitrogen mustards in the control of acute leukemia during the last decade assign little or no response to the therapy. Burgstedt recorded unfavorable results in a number of

TABLE I

Management of 7410 Cases of Acute Leukemia with Folic Acid Antagonists, Adrenal Steroids, and 6-Mercaptopurine

Agent	No. of cases	No. of remissions		No. of cases not evaluated	No. of references
		Good	Fair		
Folic acid antagonists	3114	734	695	261	182
Adrenal hormones	2269	520	759	122	176
6-Mercaptopurine	2027	422	681	282	95

children with acute leukemia who were treated with nitrogen mustards, urethan, estrogens, and splenectomy. Also, nitrogen mustard therapy proved ineffective in 20 patients of Gardikas and Wilkinson,[19] 7 patients of Rider and Warwick, 6 of Merk, 5 of Consoli, 4 of McWhirter, 3 of Wilkinson, 2 patients each of Brown and Davis, Cernic et al, Levi et al, Matthews, Mayo, Horlin and Schmitt, and Petrakis et al, and finally, 1 each of Aguire and Silva Sosa, Anglesio, Ben-Asher, Bouroncle et al, Del Dotto and Scardigli, Giordiana and Raddi, Graulich, Libansky et al, Lovisetto et al, Nabarro, Roswit and Kaplan, and Doan et al. Petrakis et al found that sulfur mustard was without effect in 4 cases of acute leukemia.

The picture of nitrogen mustard therapy of acute leukemia is not all dark, however, for some 40 clinical investigations show remissions ranging from subjective improvement to complete absence of all symptoms of the disease clinically and hematologically. Burchenal et al in 1949 described a fall in leukocyte count in 4 of 5 patients with acute leukemia after treatment with the nitrogen mustards HN2 and HN3 and some subjective improvement in 2 cases. The following year[8] they reported a fall in leukocyte count in all 15 patients in SK136 with complete remissions in 3 and subjective improvement in 8; of 10 patients on SK137, all showed a decrease in white cells, 5 a decrease in spleen, and 3 subjective improvement. Marinone[22] induced one complete clinical and hematological remission for 11 months among 10 patients with acute emocitoblastic leukemia treated with chloroethylamines, 2 complete clinical remissions only for four to six months, and a partial clinical response in a further case; in 3 acute monocytic cases there was no response, and the author warned of the danger of nitrogen mustard therapy in acute leukemia. Hibino noted 10 remissions in 42 patients treated with nitrogen mustard, and six responses in 6 patients on a combination of 6-mercaptopurine and mustard. Koyama and Toknyama reported objective remissions in 3 of 23 patients on nitromin, and fair responses in 3 of 11 on HN2. Brennan et al observed improvement in 2 of 7 patients with acute lymphocytic leukemia who were given proteinamine, a combination of plasma proteins and nitrogen mustard, but they noted no response in 1 patient with acute myelocytic leukemia who was on this therapy.

Levin and Holt treated 6 patients with acute lymphoid leukemia and 1 with acute myeloid leukemia with SK136 and induced one good clinical and hematological remission in the lymphoid group. Ohta et al employed alanine nitrogen mustard and triethylene melamine in 6 cases of acute leukemia and described two slight responses. Good objective and subjective remissions were observed by Szentklary in 12 cases of acute lymphocytic leukemia with the new nitrogen mustard, degranol, and vitamin C. Goldeck and Horst reported some improvement in 5 patients with myeloblastic leukemia after HN2 therapy. Employing cysteine intravenously prior to HN2 therapy, Weisberger et al secured excellent remissions in 4 of 4 patients, but the results in 3 were brief. Sellei et al in 1956 reduced hemorrhages in 2 of 4 patients with acute leukemia with the new mustard, BCM, and two years later Sellei and Eckhardt obtained good remissions in 5 of 10 cases of acute paramyeloblastic leukemia, but they cautioned against serious bone marrow depression. Good clinical response was noted by Bisaro and Butto in 3 patients on HN2, and Parreira and Bertelli found R48 a good adjunct to x-ray therapy in 3 cases of acute and subacute

lymphocytic leukemia. Jones et al employed nitrogen mustard analogues of chloroquinine to induce one marked and one slight response in 3 cases of acute leukemia. Good remissions were observed in 2 cases through nitrogen mustard therapy by Alpert et al and Southam, while both Macciotta and Israels et al noted almost complete remissions in 2 patients on nitrogen mustard treatment.

Beattie and Howells observed one remission in 2 patients on mustards, and Kawakita et al described partial remissions in 1 patient with acute and 1 with subacute lymphocytic leukemia on nitromin therapy. Bertola noted better responses in 4 chronic than in 2 acute cases after R48 treatments. Nitromin induced a good subjective response in 1 patient with subacute myelocytic leukemia, according to Dudik, but leukopenia developed. Nakamura used nitromin, urethan, and transfusions to obtain a brief remission in 1 case of subacute erythroleukemia, and Nakauchi combined the same mustard with lumin for a hematological remission in 1 case of subacute myelocytic leukemia. Salamone and Sanfilippo used HN2 and vitamin B_{12} to induce good clinical and hematological remission in 1 patient, while Vesin combined x rays with microdoses of chloroalkamines for a partial response. Hirota treated 1 patient with acute aleukemic myeloid leukemia and severe anemia with nitrogen mustard, vitamin B_{12}, sodium pteroyl triglutamate, and transfusions to secure a brief and partial hematological remission. A 14-month remission was described by Hofstetter after the use of mustard and urethan, and Introzzi and Ninni observed a good clinical and hematological response in 1 case of subacute leukemia treated with R48. Lonati induced a one-month remission in acute lymphocytic leukemia with CB1348, and Tazaki et al noted a partial hematological remission in 1 case of acute leukemia after HN2 administration.

Hibino employed nitrogen mustard, triethylene melamine, colchicine, etc., to obtain some remissions in 67 cases of acute myeloid and paramyeloblastic leukemia. Kimura et al in two studies reported a fair response in 3 acute myelocytic cases, and Eckhardt et al noted some remissions of six to eight months in acute leukemia after the use of nitrogen mustard, but leukopenia and thrombopenia complicated the treatment. Bauer and Erf[4] induced a number of remissions in patients with acute and chronic lymphocytic, myelocytic, and monocytic leukemias on nitrogen mustard therapy. Mayall reported a partial clinical and hematological remission in 1 case with CB1348, and Zulick employed degranol to induce a partial hematological response in 1 case of acute myelocytic leukemia.

ANTIBIOTICS

Antibiotics have been used extensively in the management of leukemia in conjunction with blood transfusions, irradiation, and other chemotherapeutic agents. The antileukemic action of the antibiotics is difficult to evaluate in such combination therapy. The present discussion is limited to the use of antibiotics alone in the treatment of acute leukemia.

Clinical. Barnard has conducted several investigations on the effect of *Streptomcyes* fermentation derivatives on acute leukemia. In 1950 he reported 18 remissions in 29 patients with acute leukemia who were given concentrates of *Streptomyces* species,

and the following year[3] he enlarged the clinical trials to 50 patients; he observed that the clinical picture was greatly improved but that the blood condition was not changed. Kobyzev[21] treated 40 patients with penicillin to produce longer survivals: 11 had hematological and/or clinical remissions, with 2 surviving one to two years, 3 for six months to one year, and 17 for three to six months; of 30 patients not treated none survived six months. Stock recorded that 3 of 15 children treated with azaserine showed partial remissions, and Ellison et al obtained brief responses in 3 of 14 children with this analogue. Huth induced five partial hematological remissions with chlortetracycline, and Tan and Burchenal noted that 1 of 7 children with acute leukemia had the stem cells in bone marrow reduced from 90 to 15 per cent. Plauchu et al employed chlortetracycline to control infections in 3 cases but recorded no change in the blood picture.

Field described some remission in 1 of 2 patients given actinomycin C, and Lacroix et al reported that this antibiotic induced a brief remission in 1 case. Gregory separated a crystalline antibiotic from *Bacillus subtilis* that caused a good remission in 1 patient with acute lymphocytic leukemia. Gernez-Rieux and Goudemand reported no response in 2 patients given actinomycin C, and Rottino et al found chlortetracycline without effect in one acute leukemia. Hibino tested antibiotics in 4 cases of acute leukemia without success. Burchenal[11] listed DON from *Streptomyces* as effective in acute leukemia, but Magill et al reported failure of this azaserine analogue to influence 10 patients in 1956 and another in 1957. Fujii et al induced a brief clinical response but no hematological improvement in 1 patient with acute lymphocytic leukemia with doses of sarkomycin.

RADIOPHOSPHORUS

Reviews. Current reviews are highly critical of the use of radioactive phosphorus in the treatment of acute leukemia. Brimi,[7] Chatterjea, and Wintrobe et al[30] listed the isotope as contraindicated.

Clinical. Half a dozen clinical reports also record no clinical or hematological improvement from P^{32} therapy. Karnaukhov concluded that radiophosphorus showed a contraindicated action in acute and subacute leukemia. Cooper found no change in 3 cases of acute monocytic leukemia and no significant effect in 8 acute lymphocytic and 8 acute myelocytic leukemias. In 1950 Diamond et al recorded no improvement in 18 patients with acute leukemia, 9 of whom were on a combination of x rays and P^{32} and 9 on P^{32} alone; the next year Diamond and Craver reported that no benefit was received in another 18 cases. Chodos and Ross observed no significant response in 8 patients with acute leukemia, and Birge et al and Marinello recorded no benefit in 1 case each, while Rogers et al noted no benefit in 2 cases. In two studies Mozharova also found little or no benefit in cases of acute and subacute leukemia treated with radiophosphorus.

On the other hand, a number of fair to complete remissions have been recorded in the management of acute leukemia with P^{32}, with survivals for longer than four years. Arini and Pavlovsky in 1957 observed seven complete and six partial remissions extending to 23 months in 20 children, with two partial responses for two and

four weeks, respectively, among 10 adults on radiophosphorus therapy; a year later Arini described one complete remission for two years among 14 cases, and 2 other patients had good responses on P^{32} plus 6-mercaptopurine plus cortisone; in another report[2] in 1958 he observed a synergistic effect in 41 patients treated with P^{32} and 6-mercaptopurine. In 1949 Pierce noticed eight clinical and four hematological remissions in 26 children with acute leukemia, the remission averaging 20 weeks for children 1 to 6 years of age and 30 weeks for 7- to 14-year-old children. In 1955 he described bone marrow remissions in 4 of 26 children for an average duration of 23.4 weeks. Bergström and Lingren in two releases reported 14 remissions in 17 patients with acute leukemia, 1 patient surviving 50 months, 1 for 10 months, and 3 for three months. Southam et al noted two fair responses in 2 patients on radiophosphorus, and Hill et al tabulated two brief responses in 10 terminal cases. Hohl described a fair remission in 1 case of subacute myelocytic leukemia, and Hibino found one good response in 6 patients with acute leukemia.

TRIETHYLENE MELAMINE

Reviews. A number of current reviews list triethylene melamine as contraindicated in acute leukemia: Arini, Brimi,[7] Chatterjea, Greenstein and Haddow, a panel discussion, and Wintrobe et al.[30]

Clinical. One third of the clinical reports of the last 10 years describe no benefit from triethylene melamine therapy of acute leukemia. Arini noted that the drug aggravated the condition in 11 patients. Asua recorded no benefit in 2 cases. Bayrd et al in 1951 and again in 1952 recorded failure of triethylene melamine therapy in 11 cases. Others finding no improvement include Medal and Silverberg and Dameshek in 5 cases each, Walsh et al in 4, Storti and Manzini in 3, Haehner et al, Rittino, and Yanguas in 2 each, and Wright et al and Palmer in 1 patient each.

In contrast to these negative results with triethylene melamine in patients with acute leukemia, a number of other investigators have reported good to fair remissions. Rundles and Barton[24] classed four responses as excellent, eight as slight, and two as inconclusive in 19 cases of acute lymphocytic leukemia, and these investigators noted that one acute myelocytic leukemia among 7 cases and one acute granulocytic leukemia responded slightly to triethylene melamine management. Koyama described five objective remissions in 12 patients lasting up to 22 days, and Beyers and Meyer also noted seven brief remissions in 12 patients on triethylene melamine.

Heilmeyer reported one complete and seven partial remissions in 11 patients, and Hibino had four fair responses in 11 patients. Marmont recorded in 1954 the results of three studies on the action of triethylene melamine on acute leukemia: in one study he and his associates noted that 6 of 7 patients had fair responses, and in a second they saw some improvement in 6 patients; in a third publication Marmont and Fusco used citrovorum factor to treat the granulocytopenia induced in 1 case of acute monocytic leukemia by triethylene melamine. Sanchez found triethylene melamine effective in 5 acute cases. Dubois-Ferriere carried out several investigations employing "oligo-metaux" (manganese, copper, cobalt, zinc, etc.) to reduce the toxicity of triethylene melamine: in 1951 he recorded brief remissions in 2 cases,

and in 1953 he described clinical and hematological remissions in three acute leukemias, and one complete and three partial remissions in 6 subacute cases; he employed a combination of triethylene melamine and x rays to induce a complete remission in one subacute case in 1951 and three complete remissions in 1952 in subacute cases. Bond et al described three good subjective responses on triethylene melamine therapy but only two fair hematological remissions, with 1 patient showing marked toxicity. Burtner et al produced one good and one fair improvement in 2 subacute granulocytic cases and a fair response in one acute leukemia (lymphocytic). Axelrod et al observed one fair remission in 3 cases of acute leukemia, and Haga et al found that 1 of 2 patients responded to triethylene melamine. Three of 5 acute cases showed some fall in leukocyte count, according to Pavlovsky and Vilasega, and fair remissions were indicated in patients of Bock et al, Shimkin et al, and Winkler and Cerny with triethylene melamine in cases of acute leukemia. Rosenthal and Lee stated that monocytic myeloblastic leukemia responded well to this therapy.

COLCHICINES

Reviews. In reviews on current treatment of acute leukemia with cytostatic substances, Schulten and Pribilla judged that colchicines were of little value, while Greenstein and Haddow listed these alkaloids among those agents whose action was contraindicated.

Clinical. More than one third of the clinical studies on the management of acute leukemia with colchicines since 1949 report little or no benefit to patients. In 1954 Leonardi and D'Agnolo recorded no benefit in 2 patients with desacetilmetilcolchicine (demecolcin or colcemid), and the following year Leonard and Wilkinson observed a decrease in the white cell count in 4 of 6 patients, but they found that all patients deteriorated steadily. Polli et al recorded no response in 2 patients with subacute leukemia after colcemid therapy, and Holly et al and Asua each reported no responses in 2 acute cases. Paolino et al in two investigations noted little or no benefit in single cases of subacute leukemia, and Schumann in two reports came to the same conclusion in acute myeloid leukemia after treatment with colcemid.

In contrast to these findings, several favorable reports have been published on colchicine therapy in acute and subacute leukemia. Stick observed a complete hematological remission in 1 patient with subacute myelocytic leukemia after colcemid therapy. In three studies Mayall recorded improvement in 2 cases of subacute, good remissions in 2 acute, and four brief remissions in 4 other acute cases after treatment with colcemid. In 1956 Hibino found that 1 of 3 cases of acute leukemia responded to colchicines, and one year later he described some benefit in 50 cases of acute myelocytic leukemia and 17 of paramyeloblastic leukemia with colcemid, nitrogen mustard, triethylene melamine, etc. Bock and Gross found that colcemid induced some hematological response in 2 patients with acute myelocytic leukemia, and Ivanov recorded brief clinical and hematological remissions in 7 of 8 cases of acute myelocytic leukemia with this same alkaloid, but there was no response in one acute lymphocytic leukemia. Grant obtained a similar reaction in two acute myelocytic leukemias but none in one lymphocytic leukemia, and Alex-

andrides et al duplicated the results in one acute myelocytic and one lymphocytic leukemia. Keibl concluded that colchicines were less effective in acute than in chronic leukemia. Dube and Srivastava noted some response in 4 of 5 cases of acute leukemia after colcemid therapy, which lasted 4, 5, 6, and 12 weeks, respectively. Vercillo and Esposito observed a fair response in 4 patients with subacute myelocytic leukemia after colcemid treatment. Moeschlin et al estimated colcemid to be one-thirtieth as toxic as colchicine, and they induced a brief remission with transfusion and colcemid in one acute myelocytic leukemia, but they observed no effect in one subacute lymphocytic leukemia.

VITAMINS

Barnard and associates have published a series of clinical reports on the action of fermentation concentrates of B_{12} on patients with acute leukemia. In 1950 he noted that the downhill course of a patient was arrested by a crude fermentation concentrate rich in B_{12}, and after two months the patient had gained 17 lb. and was back at her household duties; in two further reports that year he described another patient who had an eight-month remission on B_{12} and oxytetracycline. In 1951[3] he attributed the successful management of 50 cases of acute leukemia to the antibiotic rather than to the vitamin content of the concentrate. Giraud et al described a brief response in 1 of 3 patients on B_{12}, while Grabenko and Konaleva observed a complete remission of six months on this therapy. Welsh gave massive doses of B_{12} to 25 patients with acute leukemia, and he counted six partial remissions with 10 other patients showing subjective improvement. Harris had 1 patient with acute myelocytic leukemia in pregnancy who failed to respond to this therapy. Protti reported that yeast injections in 6 patients with acute leukemia produced no response. Hibino judged no improvement in 2 patients with acute leukemia who received the vitamin, p-aminobenzoic acid, and Kelemen and Teny saw no benefit in 1 patient on this same therapy. Gay and Montale treated 10 patients with acute leukemia with a combination of vitamin C, toluidine blue, and hesperidin methyl chalcone and induced five good responses.

URETHAN

Reviews. Erf[15] rated urethan the agent of second choice in his review of the chemotherapeutic management of acute myelocytic leukemia. In a review of 57 cases in the literature Cervini noted 20 good remissions, 15 fair, and 22 instances of no response with this agent. But Brimi,[7] Hall, and Wintrobe et al[30] rated urethan as ineffective in all types of acute leukemia. Guglielmo reported inconsistent results in 25 patients with acute leukemia who were treated with urethan.

Clinical. Wilkinson judged urethan to be of little value in 3 patients with acute leukemia, and similar conclusions were arrived at by Hibino in 3 cases, Cervini in 1 case, Rodgers et al in 1 child, and Taylor and Geppert in a newborn infant. Dustin found urethan to be of doubtful value in 2 patients with acute monocytic leukemia, and Fonseca et al noted little effect in 3 cases of acute leukemia. Spigliati described the conversion of a chronic case of leukemia into an acute form by urethan, and

Cifarelli noted that the action of the drug was contraindicated in 1 of 8 cases, with 4 patients having a brief improvement.

Better responses have been reported by other investigators in the control of acute leukemia with urethan. Gullberg recorded one good and two slight remissions in 6 patients with acute myelocytic leukemia, and one slight remission in an acute lymphocytic case. Fornana employed urethan, penicillin, and transfusions to induce some remission in 4 children with acute lymphocytic leukemia, and Muggia found some remission in one subacute myelocytic, one subacute lymphocytic, and one acute lymphocytic leukemia. Lutterotti produced one brief remission in 3 children with acute leukemia, and Moller noted a brief clinical and hematological response in a child with acute myeloid leukemia. Frentzel-Beyme used urethan to secure partial remissions for several weeks in 2 patients with acute myelocytic leukemia, and Anglesio found that 1 case of acute lymphocytic leukemia responded briefly. DeVries described a remarkable response in a child with subacute myelocytic leukemia who received urethan, aminopterin, and transfusions. Ayres treated 1 case of acute myelocytic leukemia with urethan, nicotinic acid, and B complex to register a temporary remission, and Pullen noted three months' improvement in a patient with acute lymphocytic leukemia after urethan therapy. Fritze et al described some response in 3 patients with acute leukemia after the use of urethan.

BUSULFAN

Reviews. In reviewing agents employed in the control of acute leukemia, Brimi[7] and Wintrobe et al[30] classified busulfan as ineffective. Bierman, in a panel discussion,[23] stated that the drug will produce six-month remissions in 50 per cent of patients with acute granulocytic leukemia.

Clinical. Almost one half of the clinical reports of the last decade on the use of busulfan in acute leukemia indicate little or no improvement. Wagner observed no effect in 4 cases of acute myelocytic leukemia, Arini observed none in 3 cases of acute leukemia, Storti and Pederzini found no response in 2 more acute cases, and Radford, Ramioul, Turesson, and Videbaek and Mosbech each noted no improvement in 1 patient with acute myelocytic leukemia. DeVries found busulfan of no benefit in one subacute myelocytic leukemia, and Mukhamedzianova described no response in 7 acute cases in one report, but he noted marked suppression for two weeks to three months in 4 of 5 patients with acute myeloid and 4 with subacute myeloid leukemia in another report. In two studies on the action of dimethyl busulfan, CB2348, Bierman et al noted prompt clinical and hematological benefit in 3 patients with acute granulocytic leukemia in 1957, and the following year they described one clinical and hematological remission and two hematological responses only in 3 cases. Kozxowska wrote of early hemorrhages in acute leukemia after busulfan therapy, but survivals extended from 163 to 362 days. Heilmeyer et al reported one brain hemorrhage among 8 patients with acute myelocytic leukemia on busulfan, but he classed seven of the remissions as good. Petraki et al obtained a three-week remission in 1 of 2 patients with acute myelocytic leukemia, and Galton signified a fair response for six weeks in 1 patient with subacute myeloid leukemia. Emich induced

some favorable response in patients with acute myeloid leukemia, and Bousser and Christol had 2 myeloblastic leukemia patients who responded to busulfan. Shapiro employed consecutive doses of 6-mercaptopurine and busulfan to induce a 10-month clinical and hematological remission in a patient with subacute myelocytic leukemia.

MISCELLANEOUS AGENTS

Radioactive Isotopes. Radioactive phosphorus therapy in acute leukemia has already been reviewed. In 1949 Block et al noted that 3 of 4 patients with subacute lymphocytic leukemia had fair remissions after As^{76} therapy, but they recorded no effect in 2 patients with acute leukemia. Four years later Block et al described hematological remissions in 3 subacute myelocytic leukemia cases and one clinical and hematological remission in two subacute lymphocytic leukemias. Werff observed complete clinical and hematological remissions in 2 patients with aleukemic lymphocytic leukemia who received Bi^{206}. Fellinger and Vetter observed almost no response in patients with acute leukemia after Au^{198} treatment. Ellis et al followed the uptake of S^{35} by bone marrow in 4 cases of acute myelocytic leukemia and 2 of acute lymphocytic leukemia without noting any improvement.

Phosphoramides. Farber et al[17] reported no benefit in 11 patients with acute leukemia who were treated with triethylene phosphoramide, and Shay et al in two investigations concluded that triethylene thiophosphoramide was also of no benefit in acute leukemia. Smith et al described brief clinical improvement in 8 of 12 children after triethylene thiophosphoramide treatment, but they thought death seemed to be hastened by the chemical. Koyama and Toknyama noted objective improvement in 2 of 3 patients given triethylene thiophosphoramide, and Hibino ascribed some response to this drug in 1 of 2 patients. Sykes et al reported no improvement in 1 patient with triethylene phosphoramide, but they described good objective response for two weeks in 1 of 2 patients who received diethylene phosphoramide.

Ethyleneimines. In early clinical trials with ethylene quinone, E39, Olmer recorded no improvement in 2 patients with acute leukemia, and Shanbrom and Miller described a variable response in 7 cases. In 1951 Paterson and Boland induced two hematological remissions in 2 patients with acute myelocytic leukemia, and one brief hematological response in 2 patients with acute lymphocytic leukemia who were given trisethyleimino-s-triazine, 9500; in 1953 these investigators reported a fair remission in 1 subacute lymphocytic case on 9500, and in 1954 Paterson and Kuukler found that 1,3-bis(ethyleneimino-suphonyl) propane, BEP, was without effect in acute leukemia.

Azaguanine. Colsky et al observed a marked retarding effect of 8-azaguanine in 3 of 4 patients with acute leukemia, and Bousser et al noted a slight remission in 1 of 3 patients given this compound in combination with 6-mercaptopurine and steroids. Hibino and Steinfeld et al recorded negative results with azaguanine.

6-Chloropurine. Ellison et al[14] reported three complete and eight partial remissions in 30 adults given 6-chloropurine, and they concluded that this purine was slightly superior to the more widely used 6-mercaptopurine.

Hormones. Blackburn induced transient remissions in 3 of 8 patients with acute

leukemia who were given stilbestrol, and Weicker and Schreier employed this sex hormone with aminopterin and chlortetracycline to secure brief responses in 3 children with acute leukemia. Storti noted that the course of 5 patients with acute leukemia was not influenced by intense and prolonged treatment with androgens and estrogens, but that there was some temporary change in the blood and bone marrow pictures. Meythaler and Händel observed no response in 2 acute cases after HBF386 hormone therapy, and Schwerdtfeger and Uexküll found little response in one subacute lymphocytic leukemia after using the liver extract, AF2.

Organic Peroxides. Solomides in two studies induced a remission of 18 months in a patient with myeloblastoma, and an excellent remission of four months in one acute lymphocytic leukemia by the use of organic peroxides.

Polyphenols. Lefevre and Baranger employed geranyl-hydroquinone, B158, to induce some hematological response in 2 patients.

Metal Catalysts. Dubois-Ferriere and associates conducted clinical trials on the management of acute leukemia with metal catalysts: in 1951 they found that certain "oligocene metals" diminished the toxicity of triethylene melamine and cortisone to give brief remissions in 2 patients with acute myelocytic leukemia; in 1952-1953 they conducted trials with catalysts of manganese, cobalt, copper, zinc, etc., and described clinical and hematological remissions in 3 acute cases and 1 of 3 subacute cases.

Glycolytic Enzyme Inhibitors. Black et al employed such glycolysis inhibitors as sodium fluoride, iodoacetic acid, malonic acid, and sodium azide to induce four good and three fair objective remissions, and three good and two fair subjective improvements in 11 patients with acute myelocytic leukemia, and three good and one fair objective responses and three good responses in four acute lymphoid leukemias.

Selenium Cystine. In 1955 Weisberger and Suhrland described the action of selenium cystine in inducing a rapid decrease in leukocyte counts and in the size of the spleen in 2 patients with acute leukemia, and they noted that a third patient who had been refractory to cortisone, aminopterin, and 6-mercaptopurine responded well. In 1956 they extended their studies to 2 more patients with acute leukemia with similar favorable responses, but nausea and vomiting were too severe to permit continuing the treatment.

Beta-Globulin. Injections of metal-binding β-globulin together with zinc metal caused clinical and hematological remissions in 5 infants with acute leukemia, according to Brohult.

Gamma-globulin. Faircloth had a one-month complete hematological remission in acute lymphoblastic leukemia with γ-globulin.

Alpha-peltation. Greenspan et al recorded some brief remissions in 4 patients with acute leukemia after use of alpha-peltation.

Pentnucleotide. Rodgers et al recorded that 1 in 11 patients with acute leukemia had a brief reduction in white cell count after the administration of pentnucleotide.

Desoxypyridoxine. Weir and Morningstar noted that reduction of pyridoxine by oral doses of desoxypyridoxine induced a brief response in 3 of 4 patients with acute leukemia, but Gellhorn and Jones recorded no effect in 3 cases.

Deoxy-D-glucose. Brief hematological remissions were observed by Landau et al

TABLE II

Chemotherapeutic Management of 1460 Cases of Acute Leukemia with Miscellaneous Agents

Agent	No. of cases	No. of remissions		No. of references
		Good	Fair	
Nitrogen mustards	373	46	84	69
Radiophosphorus	241	13	41	14
Antibiotics	185	6	53	17
Triethylene melamine	161	19	66	38
Colchicines	128	1	26	23
Vitamins	101	8	17	13
Urethan	54	3	24	22
Busulfan	50	12	6	18
Miscellaneous	167	19	75	42

in treatment of one acute lymphocytic leukemia and one acute myelocytic leukemia with 2-deoxy-D-glucose.

Folic Acid. Rausch found that folic acid caused anaphylactic shock in a patient with subacute lymphocytic leukemia.

5-Iodosalicylic Acid. Formijne described clinical and hematological remission in a patient with acute myelocytic leukemia who received 5-iodosalicylic acid.

Glucosamine. Marlow and Bartlett found that oral doses of glucosamine had no influence in 2 cases of acute leukemia.

Sodium Thiosulfate. Paolino and Gavosto reported death of a patient with subacute myeloid leukemia after injection of sodium thiosulfate.

Myelokentric Acid. Swan and Zelman induced a brief hematological remission in 1 patient with lymphoblastic leukemia by injection of myelokentric acid extracted from the urine of a patient with chronic myelocytic leukemia.

Dihydrotriazines. Farber et al[16] noted definite but brief antileukemic activity of dihydrotriazines in children with acute leukemia who were resistant to ACTH and/or ACTH/cortisone.

SUMMARY

1. Folic acid antagonists, adrenal steroids, and 6-mercaptopurine are the agents of choice in the management of acute leukemia. The relative merits of these three chemicals are presented in dozens of reviews. Tabulations on the results of treating 7410 patients with these leading agents are summarized in table I without citing the hundreds of clinical reports from which the data were compiled.

2. The original clinical reports are reviewed on 1460 patients treated with nitrogen mustards, radiophosphorus, antibiotics, triethylene melamine, colchicines, vitamins, urethan, busulfan, and miscellaneous agents (table II).

ACKNOWLEDGMENT

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APLASTIC ANEMIA. Both testosterone and corticosteroids were used in a new approach to treatment of aplastic anemia in 5 patients (A.M.A. J. Dis. Child. 98:293, 1959). Improvement began with early erythroid regeneration and reticulocytosis, followed by elevation of hemoglobin. Remission occurred in all but 1 case, where death resulted from gastrointestinal bleeding and overwhelming infection.

THYROXINE ANALOGUE. A thyroxine analogue, 3:5 diiodothyroacetic acid, lowered cholesterol levels by 20 to 30 per cent in 10 patients, according to Peter H. Forsham (University of California School of Medicine, San Francisco). The drug was given in doses of 15 to 30 mg. in four months of a pilot study. Patients with angina reported a significant decrease of pain, and there was a consistent lowering of the basal metabolic rate to an average of minus 15.

SECTIONING MICROTOME. An improved instrument (marketed as LKB 4800 Ultrosome by LKB Instruments, Inc., Rockville, Md.) permits automatic or manual sectioning at five different speeds. A dual illumination system enables the operator to observe sections under fluorescent lighting and also to examine the knife edge in a dark field using incandescent light. The thickness setting can be changed during cutting.

OVULATION-SUPPRESSING TABLET. An ovulation-suppressing tablet, norethindrone, gave 100 per cent effectiveness in 1600 menstrual cycles in an experimental birth control program, it was reported at the recent meeting of the Society of Air Force Internists and Allied Specialists. No pregnancies occurred during a 14-month trial period in 197 women receiving the drug. Dosage was one 10 mg. tablet per day, taken orally for 20 days a month, starting on the fifth day of the cycle. Side effects were negligible.

POSTANTIBIOTIC DIARRHEA. A specially cultured human strain of viable Lactobacillus acidophilus with sodium carboxymethylcellulose (Bacid, U. S. Vitamin and Pharmaceutical) helps to restore an aciduric intestinal flora in patients with diarrhea and other symptoms after the use of antibiotics or tainted food and water. The drug is also indicated in functional constipation, irritable colon, and diverticulosis.

HEART STOPPAGE. A method of stopping the heart for as long as 45 to 60 minutes by sending chilled blood through its coronary arteries was described at the recent American Heart Association Scientific Sessions. The heart goes into a standstill at 62 F. and at this temperature it requires only one fourth of normal amounts of high-energy substances, such as sugars and phosphates. This method appears to be safer than heart stoppage that can be induced by drugs.

ANTICHOLINERGIC PREVENTS ABDOMINAL DISTENTION. Prophylactic treatment of 400 postoperative patients with the anticholinergic ambenonium chloride (Mytelase, Winthrop) prevented abdominal distention in 398, and the drug was extremely well tolerated (Surgery 46:1043, 1959). Medication was started when the patients returned from the operating room and was continued until normal peristalsis occurred. The drug is called more "powerful" than neostigmine and "produces a lower incidence of secondary reactions."

PEDIATRIC ANTIBIOTIC DROPS. A ready-to-use pediatric dosage form of calcium di-oxytetracycline with N-acetyl-glucosamine (Cosa-Terrabon, Pfizer) is fruit flavored and packaged in dropper bottles. It is also useful for elderly and debilitated patients and others who have trouble swallowing capsules. The use of glucosamine is reported to result in higher, more consistent, and more rapid antibiotic blood levels.

MALIGNANT DISEASES. Successful treatment with cyclophosphamide of 117 patients with various malignant diseases was recently reported by Robert L. Wall and Fred G. Conrad (Columbus, Ohio). Among patients who had become resistant to other treatment, the drug proved effective in controlling about half of those with Hodgkin's disease and with leukemia. Improvement was noted in many patients with lymphosarcoma and a few with breast cancer. Cyclophosphamide is related to, but less toxic than, nitrogen mustard and can be given orally as well as by injection.

FLUOROSCOPIC SCREEN. A new fluoroscopic screen (Rad-A-Lert, Radelin Division, United States Radium Corp., Morristown, N. J.) has a special border that fluoresces red, indicating to the radiologist that radiation is escaping beyond the protective lead glass of the apparatus. The border is not sufficiently bright to disturb dark adaptation or interfere with fluoroscopy.

Atomic Philosophy and Philosophy of Medicine

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Today the word "atom" figures prominently in our thought. In actual reality, we conceive the atom to be the absolute master of life and the world, perhaps of the universe, a master that is rather prone to manifest itself more malevolent and tyrannical than life-giving. Our purpose here is to show the influence of the atomic theory on the evolution and philosophy of medicine. But in order to make this clear, it will be necessary first to tell the story of Democritus, the man who originated the concept of the atom.

Democritus was born in Abdera about 460 B.C. His father was reputed for great wealth. Democritus had two brothers. When they divided the paternal wealth, Democritus took 100 talents, which was an immense sum. For a long time he had been gazing at the continent across the sea—Xerxes' Asia, harboring fabulous Babylon. As soon as Democritus received his inheritance, he sailed across and toured Asia, Babylon, India, Persia, Ethiopia, and Egypt, to learn and to satisfy his curiosity. He saw much, and thought more. He observed human beings of various races, their various lands, and their desires and behavior. And he also observed the still, inanimate matter surrounding him in numberless shapes and sizes.

Within five years, Democritus had spent all his inheritance. He returned to Abdera with only his robe. To friends concerned about his condition, he said: "I would rather find the cause of something, than be given the Kingdom of the Persian's King."

Back in Abdera, he lived in modesty and frugality, writing prolifically on every branch of human knowledge: mathematics, physics, morals, music, poetry, medicine, agriculture, painting, grammar, phonetics, and the art of war.

(Later, at the time of the Roman emperor Tiberius, Thrassylus collected about 60 works of Democritus, which he classified in 15 tetralogies. Cicero, the celebrated Roman orator and philosopher, was fascinated by the beauty of Democritus' style, which he found equal to that of Plato. Democritus was the universal genius of antiquity.)

The years were passing, and over Democritus a law of the city of Abdera was hanging. He had squandered his paternal wealth, and for such a person there was a law prohibiting burial at death. It was a cruel law, especially for one who had lived a life of virtue and creativeness. Not that Democritus cared about his city's law, for, years before, he had retired laughing about human beings and their affairs, an attitude that earned him the title of "Laughing Philosopher." However, one day, in the theater of Abdera, he read to his fellow citizens his *Little World*, for which they gave him as a prize a great amount of money and bronze statues all over the city. Thus they changed their opinion of Democritus because he had read them something new in the knowledge of man.

Democritus' enormous production subsequently perished almost entirely, and only

small fragments survive today. We do not possess the entire *Little World*, but only some of its central points, from which we can surmise its importance and the impression it made on the citizens of Abdera. In the *Little World*, Democritus wrote of the "Being," the universe, which is eternal, unchangeable, and incorruptible. Moreover, he wrote that this universe is manifold. In other words, it is composed of many indivisible, eternal, imperishable particles. These particles he called "atoms"—the Greek word for "indivisible." These indivisible particles, he went on, because of their nature, have to come into relation with one another. Such a relation must be conceived as a motion. This motion, in order to take place, needs another factor, a certain freedom, which is the empty space outside the atoms. To recapitulate: the theory of Democritus involves a trilogy of many indivisible particles (the atoms), empty space, and motion.

Democritus explained that the atoms are extremely small material elements, imperceptible, and only to be imagined. They have no beginning but are eternal, just as their automatic movement is eternal. As they are innumerable and of immense variety and shape, they whirl in the infinity of the empty space like the particles of dust in the air. From this whirling, worlds come into being.

Democritus next had to explain the mechanism of atoms and how all these worlds are created. The whole process, he went on, takes place in the whirling. The atoms jostle one another, swing, suspend from each other. They reach this phase of suspension because of the difference in their forms. He said that atoms join together to form a world, not because they are unlike in form, but rather because they are alike. An atom, in order to couple with another one, has to be like it. Observe, he said, a crumbling wall. The lighter stones are flung together, following the same course, while the heavier ones are thrown together in another direction. Now, when a world, a star, is coming into creation, the heavier and larger of the atoms are pushed inward, while the lighter atoms are pushed to the periphery.

In the earth, he continued, the air, the ethereal skies, and fire are the light atoms flung outward, while the other components, because they are heavier, have been recomposed, or pushed inward. During this cosmogonic whirl of atoms seeking composition and order, there have been detached dense incandescent masses, which formed the constellations. Democritus explained further that everything follows the laws of "mechanics," that this implacable and wondrous succession of facts would not have been understood in his mind unless it was revealed through mechanics.

The most astounding part of his theory was that "from the atoms of earthy clay, were created our bodies!" The soul, too, he continued, is composed of smooth, fine round atoms, inhaled into the body, so that among the fleshy atoms, there are found the psychic ones, which generate the movements of our organisms. He added: "Think seriously about your specific functions, about your thinking process, your anger, your desires. How do you think they are generated? It is because of the psychic atoms. They stir up different functions according to the specific group of somatic atoms they enter; in other words, according to the organs they enter."

It was circa 400 B.C. Socrates lay dying in prison for teaching about new demons, but Socrates had never thought to stoop into his entrails to find the mecha-

nism of explaining God and soul. Democritus did. He undertook to explain the psychic phenomena through mechanical means. His theories, defined conventionally as materialistic, were not really impious toward the great awe-inspiring laws of the universe. But he was convinced that only through his theories and the mechanics of his atoms could God assume in human intelligence a little bit of palpable reality.

Such transposition of atoms from man to God, so imperceptibly performed, was the other hemisphere of Democritus' theory, immensely larger. The psychic atoms, he explained, are not to be found only in human flesh. They are scattered, permeating the universe. Psychic atoms outside of men compose the great world, made not from a single God or one spirit, but from an infinity of gods and spirits that are nothing but psychic atoms, clinging in groups of various shapes. There is a relation between the inhabitants of the great world, the gods and spirits, and the inhabitants of the little world, the human beings.

Probably, he continued, such a relation is not constant or frequent, but at times it is manifested through flows emanating from the psychic atomic groups of the great world to the psychic groups of the little world. Such intercommunication takes place in the form of oracles, dreams, and various miraculous operations. As there are benevolent gods, there are also malevolent spirits and demons.

DEMOCRITUS' INFLUENCE ON THE PHILOSOPHY OF MEDICINE

Soul, Sensation, Thought. Democritus' views on soul, sensation, and thought foreshadowed psychosomatic medicine of today: "The motion of the soul-atoms," he wrote, "actually sets the body in motion and the contact with external bodies moves the soul in the body and so causes sensation—when the soul-atoms are breathed out and death ensues, even the dead parts of the bodies have a share in sensation—there yet lurk in the body enough spherical particles to give it in a faint measure warmth and sensation."

Democritus held that soul (psyche) and mind are identical; his idea of soul should not be interpreted in a theological sense. The soul, he believed, is thought to be distributed over the body and it is the cause of sensation and movement. By "mind," he further conceived an aggregate of unmixed soul atoms situated in some part of the body and considered the cause and seat of thought. This undoubtedly represents the first attempt to think out along atomic lines what must always be the most difficult problem for any purely materialistic philosophy: how can sensation and thought and the instruments with which they are carried out be explained on a purely corporeal basis?

Elaborating on the senses, Democritus laid the foundation for belief in the main in the evidence of the senses: "Difference of taste," he wrote, "is purely subjective and is not inherent in the object; it is brought about by the 'change' in the position of the 'soul-atoms' in the tongue and palate. This alteration, which causes difference of sensation, differs in different individuals and in the same individuals at different times."

A brilliant observation of Democritus concerns the influence of emotion and thought: a thought takes place when the soul is equable in its temperature. But,

if the soul is too hot or too cold, it causes changes. He quoted Homer: "Hector lay there out of his mind (ἀλλοφρογέων)," a word that Democritus thought an exact expression of the effect of anger, which makes the soul too hot and thus incapable of thought or judgment.

Democritus' skeptical attitude influenced science and especially medicine in the sense that he pointed out the principle of dignified conservatism. But although he attached fundamental importance to the evidence of the senses, he did not surrender entirely to them.

The mind receives from the senses the information on which it builds, he wrote But when the mind denies the validity of the senses, it seems to annihilate its own validity as well. The condemnation extends to the mind and the processes of thought, so that the only solid foundation left is the true existence of the atoms and the void, though we will never have a direct cognition even of them.

In regard to knowledge, Democritus stated that there are two kinds of knowledge: one legitimate, one bastard. To the bastard, belong all these: sight, hearing, smell, taste, touch. "When the bastard can no longer see things smaller and smaller, nor hear, nor smell, nor taste nor perceive by touch, but it is necessary to investigate still more subtly, then the legitimate knowledge comes to the rescue with an instrument of investigation more subtle. . . . The way of the senses is liable to err for it deals with the shifting and changing material which produces our sensations, but the way of the mind, which deals with the ultimate realties, is 'legitimate'."

Thus, although he believed that the evidence of the senses is indispensable in understanding the realities, Democritus felt a certain distrust for the senses. His conception of life he stretched to the moral side of man's personality so that the result is but the essence of present-day mental hygiene:

"Cheerfulness" in Democritus is defined as a "state in which the soul lives peacefully and in tranquillity, never disturbed by fear or superstition, or any other feeling. A man is often prevented from doing good who has by nature much 'ill-being'." Here he is clearly referring to mental disturbance.

Democritus used the concepts of harmony and symmetry to describe further the nature of cheerfulness, which implies a balance of mind due to the absence of fear and other disturbing elements. "Cheerfulness," he continued, "comes to man through moderation in enjoyment and harmony of life. Excess and defect are apt to change and to produce great movements in the soul. Excess and defect disturb the soul and destroy its symmetry. . . . To desire immoderately is the mark of a child —not of a man. . . . It is fitting for man to pay attention to the soul, rather than the body, for perfection in the soul corrects the faults of the body, but strength of body without reasoning makes the soul no whit better."

Democritus believed strongly in education, by which "more men become good than by nature." He went as far as to state, "Nature and teaching are alike. . . . There may be understanding in the young and lack of understanding in the old; for it is not time that teaches prudence, but nurture in due season and nature."

Thus Democritus appears to have laid the foundation of a materialistic psychology and attempted to follow out with great elaboration its metaphysical implications.

In considering the influence of Democritus on the evolution of medicine, it must

be borne in mind that Democritus and Hippocrates were contemporaries. Also important is the fact that both men came from along the coast of Asia Minor, where the intellectual climate was significantly different from that of the Greek peninsula. The Ionian colonies were the home of enterprising men whose grand career was travel and commerce. Impressed by the precariousness and changeability of man's fortunes and of all things in life, the Greek mind of the Ionian colonies was torn between the transmutational possibilities of the world and the permanent realities of thought. Such a vivid sense of permanent realities, conflicting with the equally vivid sense of evanescence, gave birth to intense inquiry about the nature and origin of the world, inquiry that frequently took the sophisticated trend of atheism.

The cities of Miletus and Ephesus were fermenting with such inquiries and ideas of Anaximander and Heraclitus, and Hippocrates was nearby on the island of Kos. Hippocrates was very interested in Democritus' atomic theory, which, to Hippocrates, seemed to be the magic key to the phenomena of nature.

Hippocrates knew Democritus. In fact, it seems that Hippocrates was called to take care of Democritus, who was believed by his fellow citizens to have gone mad.

An interesting, but not surprising, fact is that Democritus himself practiced medicine. And we can see a correlation between the new medicine of Hippocrates and the theories of Democritus. Thus Hippocrates condemned any tendency to sacerdotalism, and related to Democritus' conviction of the primary importance of seeing clearly is Hippocrates' own momentous doctrine of "clinical observation."

The celebrated Galen was also from Asia Minor. His guiding belief was the fundamental importance of the evidence of the senses, which he considered the indispensable groundwork of all medical knowledge. Galen's extraordinary versatility and classic training made him a personality of immense prestige by which he imposed many of his ideas. His contemporary, Erasistratus, head of the Alexandrian school of medicine, expounded the theory of the "simple nerve," which today may be looked on as an anticipation of the cell. Now, Galen questioned whether this "vessel is a unit-mass of living matter, or merely an agglomeration of *Atoms* subject to mechanical laws." And later he wondered "whether this small elementary nerve is continuous or whether consists *of many small bodies such as those assumed by Democritus.*" So we find Democritus' concept of atoms well established into the theory of the cells of the human organism.

It might be stated that Democritus' atomic theory influenced the philosophy of medicine because his philosophy, as representative of Hellenic culture, emphasized freedom of thought, observation, and investigation, which alone can guarantee to medicine the possibility of development and without which—as we are taught by history—there cannot be any true progress of science.

But what constitutes progress in the case of science and in the specific instance of medicine? Is it an unveiling of ideas whose significance is preordained by a set attitude of mind, or is it an unfolding of concepts along the trajectory of freedom and imagination, a trajectory that spreads into the unknown remote beyond?

It is understood that conscience, thought, sentiments, aspirations toward truth, beauty, justice and the base passions as well—in a word, all manifestations of life—derive from the multiform reaction of matter. But why and how? This is the

problem of the origin of life, which cannot be solved without understanding the atom.

The atom is not something alive, but it contains the immaterial potentialities that will give birth to organic cellular matter of all the vital phenomena. The atom encloses the virtuality from which will emerge life in its physicochemical, mechanical, and moral aspects, in other words, knowledge, conscience, instincts, intellectuality, spirituality.

This immaterial active principle in the center of the atom generates not only the physicochemical affinities, the molecular cohesions of bodies, and the universal gravitation, but also the stability and duration of things and beings. It is in itself the reason of the universe and the causality principle of the most rudimentary reactions and most exalted actions and thoughts of man.

Similar considerations to which we are led by the study of the atom are directly related to the mystery of creation and also to the source from which medicine draws the material to shape its spirit and future.

If human personality in its twofold aspect, physical and moral, is the subject of medicine, then the evolution of this subject as understood through the unfolding properties of the atom becomes the immediate concern of medicine, not only regarding any abstract implications, but also concerning the practical aspects of medicine.

One focus of medicine's attention at present are the viruses, which once more takes us back to Democritus. "Even stones have souls," he said. Today, it is accepted that there are no fundamental differences between nonliving and living things. Viruses are considered molecules and cells.

Yet, we still must determine what the attitude of medicine should be in approaching the problem of man's personality. Is medicine going to function by considering the phenomena of the organism, the result of physicochemical reactions brought about by atomic variations, a source intangible but nevertheless material, or is medicine going to focus on something beyond electrons and protons?

Democritus had appealed to interactions between atoms of things and atoms of soul for the appearance of "qualitative richness." In other words, without the intervention of soul atoms we have no quality. And, in the world of medicine, quality would undoubtedly mean a healthier, more harmonious psyche from which the organic-somatic filaments would appear to be appended. Psychosomatic medicine, based on the interplay of psyche and soma (soul and body), represents the modern and evolved spirit of medicine. Yet, even in its details, it is not more modern than Democritus.

The fact is that medicine, by conquering cancer and viruses and mastering at will the length of life by a complete understanding of the mechanism of the atom's histology, will assume a role unpredictably novel. Such novelty may consist of the fact that we attribute every behavioural expression to atoms and that we also wield a mastery over them. This mastery will arrange things at will and render similar operation a sort of "push-button" order. An implication of this sort will eventually dispense with the painful process of discipline and conscious cultivation of values in the instance of the individual. But also, when confronted with human personality,

medicine will no longer carry the conscience of a lofty duty, but an impersonal, precise, and mechanical role.

This seems to be the consequence of Democritus' atomic conception of matter, though previously we noted that he did not entirely surrender to the evidence of the senses.

Democritus, from the entrance of history's gallery, threw an idea that rolled down the centuries. Men of all times grappled with it, to unravel the intriguing mystery. Today, the human beings who are about to extricate the end of the rolling spool are reminiscent of a frightened, exasperated pack of wolves rather than a gathering of men who stand in awe, serenity, and gratitude.

We have mentioned that Democritus retired at Abdera. He was called the Laughing Philosopher because he used to laugh about the doings and fate of man. Did a distant vision about his theory prompt his laughter? If so, it was a cruel joke on Democritus' part to uncover to our eyes this terrible secret of nature, and then lean back laughing. We think we can hear the distant roar of his laughter, which at times reverberates as though through "Hades' vast vaults."

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Course in Electrodiagnosis and Electromyography

A course in electrodiagnosis and electromyography for physicians only will be conducted by the Department of Physical Medicine and Rehabilitation, New York Medical College, starting June 6. The curriculum will be as follows: introduction, history of electrodiagnosis, physiology and anatomy, electrophysiology, electronics, techniques, application of techniques in various clinical conditions, special techniques, future clinical and research implications. A tuition fee of $150.00 will be charged for the course.

The Epic af Medicine (VI)

WHILE SCHEHERAZADE TELLS HER TALES*

(Arabian Medicine, 732-1096)

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And on the 436th night, Scheherazade began the tale of Abu al-Husn and his slave girl, the fair Tawaddud.

A "rose of crystal and silver, scented with sandalwood and nutmeg . . . with eyes like gazelles' eyne . . . cheeks like anemones of blood-red shine . . . and hind parts heavier than two hills of sand," Tawaddud prevailed upon her impoverished master to sell her to the caliph Harun-al-Rashid. Once in the presence of the caliph, Tawaddud offered to answer all questions on "syntax, poetry, jurisprudence, exegesis, philosophy, the divine ordinances, arithmetic, geodesy, geometry, ancient fables, the Koran, the exact sciences, medicine, logic, rhetoric and composition, the lute, dancing and fashions." The answers of this fabulous creature to the questions on medicine, anatomy, and physiology afford a revealing picture of Arabian medicine in its golden age.

Arabian medicine was Persian and, indirectly, Hellenic in origin. Long before the Arabian conquest there lived in Constantinople one Nestorius, an eloquent Aramaic priest who was banished to the Libyan Desert, because he dared maintain that the Virgin Mary was the mother of Christ, not of God. In a distant oasis, in the green shades of the towering palm trees, Nestorius and his followers, having paid dearly for their aspirations to heal man's soul, turned to healing man's body. Disillusioned with their own times, the Nestorians cast their eyes back to classical Greece and drank avidly of the medicophilosophical waters of the Greco-Roman school. Later, generous with their new knowledge, they poured the ancient Hellenic nectars into Syrian vessels, translating Greek medical works into Syrian and establishing the famous medical school at Jundishapur and others in various Persian towns. Thus the Nestorians revived in Persia the lost luminous Hippocratic-Latin tradition. Later, when the Arabs conquered Persia, they suddenly found their shepherds' pouches filled with the medicophilosophical treasures of the Greeks recorded on old Nestorian parchments.

A young and ardent Semitic people, the Arabs, who for centuries had been content to roam the burning sands of Arabia, spurred on by the monotheistic preachings of

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Mohammed, set out in the seventh century on a fabulous historical cavalcade, in the course of which their scimitars carved out an empire that stretched from China to Spain, including northern Africa. Centering their power in the caliphates of Bagdad and Córdoba, they created the mighty Saracen civilization, which was to perish in the thirteenth century with the sack of Bagdad by the Tartars and the expulsion of the Arabs by the Turks in the East and by the Spaniards in the West.

The Arabs never forced their religion on the peoples they conquered; they only required that the Koran be recognized as the vehicle for the divine word, and since the sacred book was written in Arabic, the conquered peoples had to learn the tongue of the victorious invaders. Thus the vast Moslem empire came to be united by one single language. Before Arabic became the official language among learned men, Greek, and later Syriac in western Asia, had been the preferred language. But from the ninth century on, both the humble rug vendor in the public market and the haughty physician at the caliphs' courts spoke in Arabic.

The only other term imposed by the Arabs upon the conquered peoples was the surrender of old Greek manuscripts. What splendorous times, when even beneath the warrior's mail beat a heart avid for culture! When Michael III of Constantinople was defeated, the penalty imposed on him was that he send a caravan of camels loaded with ancient manuscripts to Bagdad. The pen was mightier than the sword.

The Abbasside caliphs wisely recognized the importance of translating into Arabic their vast Greek cultural war booty. Never in history have translators played as important a part as they did at the beginning of Islamic expansion. Heroes of this period were the famous Syrian and Coptic families of translators, the Bakhtîshû and the Mesues, and that prince of translators, Hunain, also called Joannitius. Thanks to these men, the Arabs, whose total knowledge at the end of the eighth century consisted of a translation of a Greek medical book and a handful of alchemy books, before the end of the ninth century had become acquainted with all the Greek sciences.

The glory of Greece vanished and the might of Rome destroyed, there remained only the work of these Arabian translators and that of the Byzantine copyists to span a bridge of light across the thousand dismal years that elapsed between the fall of the Roman Empire and the jubilant explosion of the Renaissance.

Schools of medicine flourished in Samarkand and Bagdad, Isfahan and Alexandria, Córdoba, Seville, Toledo, Granada, and Saragossa. Through almost the whole of the ninth century, medical practice in Bagdad was in the hands of foreign Christians, whose skill was considered superior to that of the Arabs.

The eastern caliphate, or caliphate of Bagdad, was illuminated by the presence of four Persian luminaries: Al-Tabari, Rhazes, Haly Abbas, and Avicenna.

Al-Tabari wrote *Paradise of Learning*, a paper chest scented with Arabian vegetable drugs—tamarind and sandalwood, nux vomica, Persian vetch, gum arabic. For, more than by any other branch of medicine, the Arabs were fascinated by pharmacology.

Rhazes, "the Experimenter," who alternately cultivated the gusla and medicine, head of the great hospital of Bagdad, physician to caliphs, proponent of a meager therapeutic arsenal in contrast to the abundant pharmacological fare served at the banquets of Arabian chemistry, was also a great compiler. His *Liber Continens* gained

him much fame. It also lost him his sight. It is said that a hierarch whom he had offended ordered that he be beaten on the head with his own book until one or the other broke. Rhazes' head broke first.

To Haly Abbas, a Zoroastrian magician, we owe a *System of Medicine*, perhaps the best and most lucid Arabian medical work and the first to be translated into Latin.

With even greater brilliance shone Avicenna, the Persian Aristotle, prince of Arabian physicians, devourer of libraries, unparalleled dialectician in Moorish, Arabic, and Latinity, statesman by day, ready at night to forsake deep philosophizing for light-hearted feasts, well versed in old wines, chaser of fresh maidens, now wielding the vizier's staff, now turning to the guitar, the gusla, and the pen. Avicenna wrote the *Canon Medicinae*, the most famous medical book in history, a medical Bible whose million words made its author world dictator of medicine until Vesalius, supplanting for six centuries the medical dictatorship of Galen. In the *Canon*, epitome and summary of Greco-Latin medicine, the thorns of dogma bristle on the roses of science. The backbone of Arabian medical thought, it recommended the cautery instead of the surgeon's knife, for the Arabs had a horror of dissecting the human body. Today, a thousand years later, the principles of Avicenna's *Canon* still continue to heal the sick of Persia.

In the western, or Cordoban, caliphate the arts and sciences flourished, but except in mathematics and literature, the Arabs were compilers and transmitters, rather than creators. Their architecture, rich in domes and ornate surfaces, derived from Byzantium; their cloistered patios, from Rome; their medicine, from Greece by way of Syria and Persia. Above all, the Arabs catered to the pleasures and comforts of the body, to which they subordinated even the soul. Their cities boasted glass windows and street lamps—reflections of their yearning for clarity and light—and abounded in enchanting gardens, redolent of exotic flowers and resonant with the murmuring of brightly tiled fountains.

The caliphs were generous patrons to scholars, and next to their deep-in-sensuous-shadows seraglio stood their libraries lined wall to wall with yellowing parchments. Córdoba alone had fifty hospitals, seventy public libraries, and the most renowned university in Europe in the tenth century. In the library of Alhaquen II alone there were nearly three hundred thousand volumes, bound in leather and gold, containing in the sinewy and virile Arabic language the whole of Arabian knowledge. The Arabs assiduously cultivated astrology and alchemy, the mother of Arabian polypharmacy. There were numerous families of physicians, such as that of Avenzoar, which followed the medical tradition for three centuries. Next to sandalwood-scented mansions, the Arabs built hospitals, which, in Andalusia as in Bagdad, were also refuges for the insane and the destitute. And everywhere water, so prized by them, spurted and spun into braids of crystal for the baths and ablutions that were as indispensable as prayers. They led an indolent life in their flower-laden gardens, sipping fruit- and rose-flavored drinks, watching the golden dance of the bees from flower to flower, while deep in myrtle and basil, rosebays and gillyflowers, the water gurgled in the tiled fountains.

Medicine was taught privately, while a general education was acquired in a

medressen, or cultural center, attached to the mosques. Medical students learned first the art of mortar and pestle from an apothecary, then sought to enter the service of an experienced physician with an extensive library.

They considered the heart the sovereign of the body; the lungs, its fan; the liver, its guardian and the seat of the soul; the pit of the stomach, the seat of pleasure. They combined alchemy with ancient Chaldean magic, establishing "correspondences" between stars, spirits, metals, and the anima mundi. Seeking the elixir of life and eternal youth, they founded medicopharmaceutical chemistry; searching for potable gold, they discovered aqua regia. Led astray by Galenic polypharmacy and by Aristotelian dialectics, the Arabs also believed that it was sinful to open the human body and so halted progress in anatomy.

The giants of the Cordoban caliphate were four. The Cordoban Albucasis the surgeon, the Arabian Vesalius, wrote *al-Tasrif*, beacon light of European surgery until the time of Paré. Defying tradition and the Koran, he illustrated his texts himself. He adopted the iron cautery, tied arteries, described the position for lithotomy, practiced transverse tracheotomy, and differentiated between goiter and thyroid cancer. The Sevillian Avenzoar, an anti-Galenist, a ladies' man, physician to Almohad caliphs, was perhaps the greatest clinician of this period. He despised Avicenna's *Canon* and was the most Hippocratic among the Arabian physicians. The Cordoban Averroës, Aristotelian and pantheistic philosopher, perhaps the initiator of medieval scholasticism, physician to a caliph in Marrakech, influenced even his opponents with his subtle heterodox philosophies. The wandering Cordoban Maimonides, the greatest Jewish humanist and philosopher of the Middle Ages, whose services Richard Coeur de Lion tried in vain to secure, physician to the Sultan Saladin, practiced medicine in Egypt, whither the intolerance of the Almohades had forced him to flee. By basing theological principles on reason, he did for Judaism what Averroës had done for Islamism and St. Thomas would do for Christianity. Devoted to medicine as an art, he studied patients, not diseases, reconciling reason and faith, rejecting astrology, and left as heritage his wisdom-permeated *Guide for the Perplexed* and his priceless axiom: "Teach thy tongue to say I know not, and thou wilt progress."

The Arabian legacy to civilization was vast and varied, comprising fireworks, as colorful and explosive as the Arabian temperament, exquisite gardens and palaces that have endured to this day, geology and algebra, ceramics, textiles, botany, medical chemistry, and the first materia medica. The Arabs discovered various acids, nitrate of silver, benzoin, camphor, saffron, sublimate of laudanum, and anesthetics; developed the alchemical techniques of crystallization, distillation, and sublimation; and created the first pharmacies, which displayed their vast polypharmacy and their medical panacea: the mellitums, together with numerous vials containing all sorts of weird things, from fetuses to frogs and scorpions. These pharmacies served also as meeting centers where all sorts of information and news were exchanged and discussed. The Arabs enriched man's language with such words as "drug," "alkali," "alcohol," "sugar," and many others. Their search for the philosopher's stone led them to advance laboratory methods and to invent the art of compounding prescriptions, sirups, juleps, poultices, electuaries, pills, powders, and alcoholates,

which they kept in majolica jars, magnificent examples of pottery, embellished with fruits and leaves because at first they were used for preserves.

Above all, the Arabs built splendid hospitals, such as Al Mansur in Cairo, equipped with wards for both sexes, murmuring fountains to cool feverish limbs or soothe restless minds, libraries, dispensaries, reciters of the Koran, music for the sleepless, singers, and storytellers. Discharged patients were provided with money so that they need not go to work immediately. Their high rate of blindness from trachoma led the Arabs to make a thorough study of the human eye, and to progress markedly in optics and the removal of cataracts, the latter operation being symbolic of their thirst for more light.

Arabian medicine, reflecting the Hellenic sun on the Arabian crescent, illuminated the medieval darkness until the dawn of the Renaissance.—*Félix Martí-Ibáñez, M.D.*

"That Skill That Death Loves Not"

Surgery, "that skill that death loves not" (as it was called in the thirteenth-century *Regimen sanitatis Salernitanum*), whose first example, a "costectomy," took place in the Garden of Eden, is turning from individual art into team science. In prehistory's dark millennia, surgery was born as an instinctive reaction to accidents demanding immediate and individual action, such as stopping a hemorrhage, splinting a fracture, or binding a wound. Man before he truly became a surgeon was first an operator, that is, an empirical expert in repairing with his hands and tools the effects of traumas. Many centuries ago man already bored with a stone scalpel into human skulls, though the purpose of such trephining was not to penetrate *into* the skull but to let *out* the invading demon that possessed the patient. When surgery became rational in Greece and Rome, empirical purpose instead of magic ritual began to guide the use of the scalpel. But the medieval night, fraught with demons and witches, once again shrouded the scalpel's point in the cobwebs of mysticism.

In the late Middle Ages and the Renaissance a new surgery was born in the teachings of the great medical masters, whose word, skill, and example finally snatched this art from the hands of barbers, bathkeepers, and executioners. Later, Ambroise Paré gave surgery the humane touch, just as John Hunter gave it science; Lord Lister, technique; and Theodor Billroth and Harvey Cushing, art.

Modern surgery began when, with the conquest of surgery's two most ancient enemies—hemorrhage and pain—the operating surgeon no longer had to fight against time. Later came the defeat of other fatal adversaries of surgery: post-operative infection, malnutrition, psychic trauma, and physical exhaustion. Only when hemostatics, analgesics, anesthetics, ataraxics, antibiotics, vitamins, minerals, and physiotherapeutic equipment became available, banishing the danger of bleeding, pain, shock, infection, malnutrition, and invalidism, could the surgeon truly dedicate himself to the development of surgery.

Paradoxically, it was the two World Wars and various lesser wars in the present century, and the increase in accidents owing to improvements in modern locomotion and industry, that stimulated surgical progress. The surgeon has sought in chem-

istry and physics new and increasingly more subtle substances and instruments for exploring the lesions of the human body. No longer compelled to watch the clock in operations or the calendar in convalescence, the surgeon can now save his energy more for brainwork than for handwork. Today, surgery is less and less a heroic emergency operation and more and more a well-thought out scheme of *physiological* repair.

Today the patient's psychological, surgical, and nutritive traumas are reduced to a minimum. The three fundamental objectives of preoperative preparation and postoperative care are now: to prevent infection, to eliminate pain and hemorrhage, and to maintain a normal metabolism. Operations are based on an accurate diagnosis, depending on clinical examination, laboratory tests, intraorganic visualization, and roentgenograms. Analgesics, from codeine to meperidine, are constantly being developed and adapted to different types of operation; antibiotics prevent infection; anticoagulants prevent unwanted blood changes; vitamins, fluids, electrolytes, and amino acids forestall dehydration and malnutrition in the patient; physiotherapy and early ambulation promote recovery and rehabilitation.

Ultrasound scalpels, "chemical scalpels" of proteolytic enzymes such as plasmin, and other new types of steel scalpels, some smaller than a fingernail, are now employed. Special lighting arrangements, electronic and radar devices for pinpointing organic processes, radioactive tracers, artificial lungs, kidneys, and other organs are also used. Countless are the methods and instruments, from ballistocardiography to gastroscopy, and from the dermatome to the "cyclone" knife. Daring techniques follow one another in a spectacular procession, for instance, resection of the aorta in the treatment of an aneurysm, or leukotomy to sever the thalamic centers (still the nervous tissue lair of our primitive ancestors) from the "civilized" prefrontal lobes. A neurovegetative block is obtained by means of "lytic cocktails," which send the adrenal-pituitary couple off on a "chemical holiday," while the shock of surgery is reduced by artificial hibernation. Electrical stimulation of some temporal lobe zones revives forgotten memories.

All these and many other facilities, such as blood banks and stocks of individual organs, ultraviolet rays, advances in the chemistry of gases and the physics of thoracic pressure, which have furthered progress in anesthesia, oxygen tents, hospital air conditioning to prevent the evaporation of organic humors—all these facilities moved the Surgeon-General of the United States Army to say once: "More than 96 per cent of the wounded who reached medical care in World War II lived."

Like a traveler on the march, surgery approaches a new horizon with each fresh dawn. Surgery is no longer "the failure of medicine," as someone once said, but its partner. Although medicine has wrested from surgery many fields of work (such as mastoidectomies and other otological infections, or digital and instrumental manipulation in urinary infections), surgery, on the other hand, with its successful treatment of cerebral embolisms, arteriosclerosis limited to vascular zones, coronary occlusions, valvulopathies, and even certain neurological diseases, has replaced medicine in certain affections previously susceptible only to medical treatment. The surgeon is no longer the Renaissance adventurer who set out to explore the human body with the same enthusiasm with which navigators explored the *terra incognita* beyond the

seas. Nowadays he explores man's inner space with the same insight and astounding accuracy that is shown by physicists exploring outer space. The surgeon's manual skill is supplemented and guided by the light of his scientific knowledge.

The drama of the amphitheatre, however, remains unchanged. Just as the *matador*, alone with the bull in the arena in that dramatic instant that decides the *corrida*, has his "moment of truth," so must the surgeon also (the only man to use cold steel in a mission of healing and mercy) pass through the crucial moment. Now, as thousands of years ago, the surgeon, all alone with his patient on the mysterious threshold of salvation or death, depends entirely on his skill and wisdom and must also suffer his "moment of truth," from which so often his scalpel emerges, as Ambroise Paré said, like a merciful emissary of God's goodness in healing by the hand of man.—*Félix Martí-Ibáñez, M.D.*

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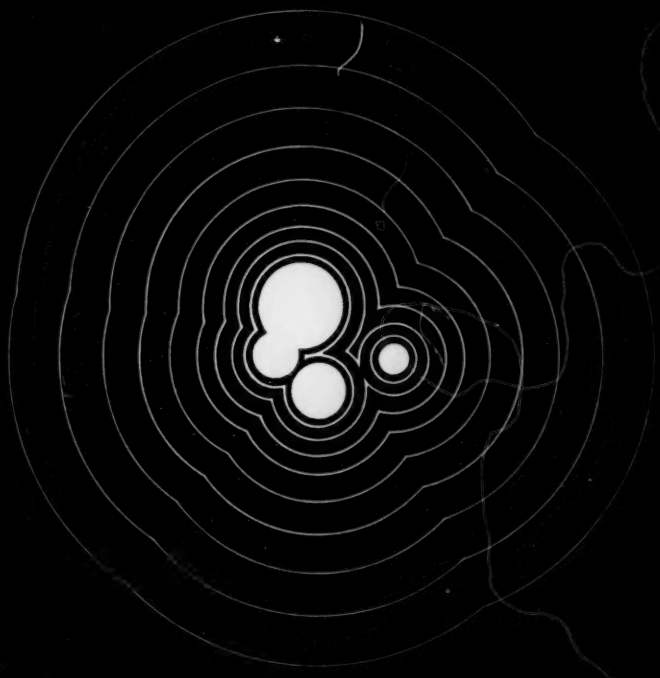

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